Report of the GPRA Assessment Working Group of the Advisory Committee to the Director, NIH

Assessment of NIH Research Program Outcomes

This page left intentionally blank

CHAPTER 1

The Government Performance and Results Act: A Brief Primer

Introduction

In 1993, the 103rd Congress passed the Government Performance and Results Act (GPRA), and President Clinton subsequently signed it into law (Public Law 103-62). The GPRA seeks to improve the effectiveness, efficiency, and accountability of Federal programs by requiring that Federal agencies set strategic goals, measure performance, and report on the degree to which those goals were met.

As part of the GPRA *strategic planning process*, an agency identifies long-term goals and objectives related to the agency mission and describes the strategies through which those goals and objectives will be met. Strategic planning is also the starting point for agencies to set more specific, short-term goals for their programs and to measure the performance of the programs in achieving those goals. The *annual GPRA performance plan* provides the direct linkage between the strategic goals and what managers and employees do day-to-day. It sets out both the annual performance goals and the performance measures that will be used to assess its progress. Finally, the GPRA requires that each agency submit to the President and Congress an *annual report on program performance for the previous fiscal year*. The first of these reports, on program performance for fiscal year 1999 (October 1, 1998-September 30, 1999), is due by March 31, 2000, and subsequent reports are due by March 31 for the years that follow. In the report, an agency compares its performance with its performance goals. If a goal is not met, the report is to explain why and how this will be addressed. The report also includes the summary findings of program evaluations completed during the fiscal year covered by the report.

NIH Response to GPRA

The NIH is engaged in all three phases of GPRA=strategic planning, setting performance goals, and measuring/reporting on performance.

For the strategic planning component of GPRA, an agency is defined as a cabinet-level department or independent agency. This means that for GPRA purposes, NIH is not considered an agency. Rather its parent organization, the Department of Health and Human Services (DHHS), is the agency that must develop a long-term strategic plan. The DHHS Strategic Plan integrates the program activities of all of its component operational divisions, which include, for example, the NIH, Food and Drug Administration, and Centers for Disease Control and Prevention. NIH=s core programs (described below) broadly support the goals and objectives set

forth in the DHHS Strategic Plan and the NIH has provided considerable input into the development of the DHHS Strategic Plan.

NIH also engages in annual performance planning and reporting under the GPRA, and this is done not at the Department level, but directly by NIH. Preparation of NIH=s annual GPRA performance plans and annual GPRA performance reports is the responsibility of the Office of Science Policy within the Office of the Director, NIH. GPRA documents are formally submitted by NIH in conjunction with the normal cycle of budget document submissions throughout the year. In compliance with the requirements of the GPRA, the NIH has prepared and submitted Annual Performance Plans for Fiscal Years 1999 and 2000. The FY 2001 Performance Plan is also being developed.

NIH GPRA Performance Plan. For purposes of GPRA planning and assessment, the NIH has aggregated and categorized the mission-related activities of all its Institutes, Centers, and Offices into three core program areas: Research, Research Training and Career Development, and Research Facilities.

- The *Research Program* encompasses the full spectrum of medical research. This includes, for example, basic, translational, and clinical research; population-based studies; behavioral research; and health services research. In addition, the timely dissemination of medical and scientific information is a key component of the Research Program.

- The *Research Training and Career Development Program* addresses the need for a steady supply of creative and well-trained personnel to conduct medical research. The primary goal of NIH=s support and programs in graduate training and career development is to recruit, train, foster, and retain highly-trained investigators who are likely to perform research that will benefit the Nation=s health.

- The *Research Facilities Program* ensures that the scientists we support have modern, efficient, and safe facilities in which to conduct their work.

For each of these three core program areas, the NIH has identified expected outcomes, major functional areas, specific performance goals, and annual targets within its GPRA performance plan. The performance goals in NIH=s annual performance plans address both the long-term, intended results or outcomes of NIH core program activities and the management and administrative processes that facilitate the core program activities and lead to the achievement of outcomes. For example, within the Research Program, outcome goals include increased understanding of biological processes and behaviors, as well as improved prevention, diagnosis, and treatment of diseases and disabilities. Management and administrative processes include communication of research results, technology transfer, priority setting, grants administration, and peer review.

NIH=s Annual Performance Plans include performance goals that can be assessed through the use of objective/quantitative measures as well as performance goals that require descriptive performance criteria. The vast majority of the approximately 50 performance goals NIH has identified have objective/quantitative targets.

A small subset of the annual performance goals, related to the NIH Research Program, are more qualitative in nature. The NIH has concluded that strictly numeric goals and measures are neither feasible nor sufficient to capture the breadth and impact of NIH=s Research Program. In situations such as this, the GPRA provides an avenue for an agency to define performance goals that rely on criteria which are more nearly descriptive in nature [Aalternative form@ assessment, Sec. 1115 (b)(1)].

This applies to five of the seven NIH Research Program outcome goals:

- Add to the body of knowledge about normal and abnormal biological functions.
- Develop new or improved instruments and technologies for use in research and medicine.
- Develop new or improved approaches for preventing or delaying the onset or progression of disease and disability.
- Develop new or improved methods for diagnosing disease and disability.
- Develop new or improved approaches for treating disease and disability.

Assessment of Qualitative Goals. As part of this >alternative approach= to assessment, NIH is required to develop an independent review process for assessing performance related to these qualitative goals. In the broadest of terms, the assessment involves gauging the extent to which NIH=s stewardship of the medical research enterprise leads to important discoveries, new knowledge, and improved techniques that are applied to the development of new diagnostics, treatments, and preventive measures to health and health-related quality of life.

The approach described belowCthe use of descriptive performance criteria and an independent review panelCis consistent with what other Federal agencies with research missions (such as the National Science Foundation) are proposing and with the findings of a recent National Academy study on how research can best be evaluated in the context of GPRA.

NIH GPRA Performance Report. For the objective/quantitative goals, data provided in the performance report will allow a direct comparison between the performance goal and the actual performance level. Or, in those cases where the goal is to complete an action, data will be provided that demonstrate the action has been completed. Where a performance goal is not met, or is partially met, a discussion of why the goal was not met will be provided. Additionally, revised plans or schedules for meeting unmet or partially met goals will be identified, unless it is determined that it is infeasible to meet the goal.

For the five qualitative goals related to the NIH Research Program, the NIH has developed an special assessment process, described in more detail below. *The results of that assessment are described in this report,* which is part of the overall NIH GPRA Performance Report.

Assessment of NIH Research Program Outcomes: Challenges

Agencies whose missions include basic and clinical research face unique challenges in developing the objective/quantitative performance goals preferred under GPRA. Although the word Ascience@ comes from the Latin *scientia* meaning Aknown things,@ scientists and the practice of science exist because of what we do not know. The aim of science is to move the unknown into the realm of the known and then, with a greater store of knowledge, begin again, as if advancing a frontier. This basic truth about science makes it different from other enterprises. Science deploys its resources and talents to explore new areas and produce fresh results, which are not endlessly replicated, but that pave the way for future and different explorations.
The many disciplines of medical research contribute to the store of knowledge and to one another, and all deserve exploration and funding. Discoveries that will increase our knowledge of the causes, progression, and treatment of asthma, for example, may stem from epidemiological, clinical, and molecular research, conducted by teams of investigators building on the discoveries of their predecessors, including those in other fields.

Since it is impossible to know with certainty which area will produce the next important discovery, the community of science, of which the NIH is a part, has to be open to all ideas. No one field has all the answers, but investigators in many different fields can ask the questions that will provide more knowledge about disease and health.

It is a striking characteristic of science that it requires both creativity and precision to generate ideas and results. The precision with which investigators pursue an idea, however, cannot alter the inescapable truth that many of the results of research are unpredictable, given the pursuit of unknown things. It requires an special kind of ›scientific open mindedness= to analyze results and not simply conclude that an experiment failed because it did not yield an answer to the original question, but rather to recognize the potential implications of an unanticipated finding for other important biological questions. For example, the investigator examining patients with ataxia telangiectasia, a rare genetic disease, who discovers something new about the origins of cancer has not Astumbled@ on a discovery, but rather has put himself or herself in a position to make the discovery, to recognize its unexpected significance, and to bring it into the realm of known things which would not have happened otherwise.

Although much of NIH funding supports research projects that are of obvious relevance to specific diseases and public health, it also places a high priority on fundamental, untargeted research. Initially, and sometimes for many years, it is unclear what role this research may play

in improving health, but history has shown many times over that a basic research finding might prove to be a critical turning point in a long chain of discoveries leading to improved health. Basic research programs can be evaluated meaningfully on a regular basis, but ultimate outcomes of research into fundamental processes are seldom predictable or quantifiable in advance.

This unpredictability has three important implications. First, science is by nature structured and self-correcting, so that either a predicted or an unforeseen discovery has the advantage of adding to basic scientific knowledge and giving new direction to further inquiries. This self-correction, carried out under public scrutiny of the results, means that science operates in a dynamic environment. The self-correcting nature of scientific inquiry requires a multiplicity of investigative approaches and the ability to adapt quickly to change. Importantly, because the system is inherently self-correcting, Abad ideas@ do not get a second chance. On the other hand, failure is allowed. Science could not proceed otherwise.

Second, science and its administrators must constantly reevaluate and often change their priorities in light of new discoveries. Very simply, science itself sets its priorities as it refreshes and enlarges knowledge: the more that is known the better are the next set of questions to be asked. Thus, while goals may not change, the route to fulfilling them might well be amended along the way. It is by asking as many questions as can be formulated and by prudently spending resources that the most promising medical priorities can be pursued. As priorities shift and acquire sharper focus, scientists are better able to look across the spectrum of biological and biomedical disciplines and of diseases. Constantly renewed knowledge enables scientists to examine, for example, the effects of pesticides not on one kind of cancer but on all cancers. Moreover, the answers to fundamental questions such as Awhat turns genes on or off?@ will lay the groundwork for targeting the diagnosis and treatment of chronic diseases such as Alzheimer=s disease, cancer, and diabetes.

Third, tracking the many aspects of fundamental science is a daunting challenge that must capture quantitative, qualitative, and institutional dimensions. History shows us that basic research often leads to outcomes that were unexpected or took many years or even decades to emerge. Thus measures of the practical outcomes of basic research usually must be retrospective and historical. It is normal and necessary for basic research investigators to modify their goals, change course, and test competing hypotheses as they move closer to the fundamental understandings that justify public investment in their work. Therefore, it is necessary to evaluate the performance of basic research programs by using measures not of practical outcomes but of performance, such as the generation of new knowledge, the quality of the research performed, and the attainment of leadership in the field.

By supporting disease-related and basic research projects simultaneously, NIH can achieve both near-term improvements in the diagnosis, treatment, and prevention of specific diseases as well as long-term discoveries in basic science that in time will produce great advances in our ability to

understand, treat, and prevent disease or delay its onset. The challenge is to devise assessment strategies appropriate to the creative processes of science and innovation.

Assessment of NIH Research Program Outcomes: Process

GPRA Assessment Working Group

Rather than convene a special ad hoc committee solely for purposes of GPRA assessment, NIH determined that the review could appropriately be carried out by a Working Group of the Advisory Committee to the Director, NIH (ACD). This Working Group was comprised of representatives of two standing NIH advisory committees which had already been established to provide advice across a broad range of topics. All members of the ACD and NIH Director=s Council of Public Representatives (COPR) were invited to participate in the assessment process. To facilitate attendance and reduce travel costs, the assessment meeting was scheduled for the day after the planned COPR meeting in October, 1999.

Due to scheduling conflicts, not all members of the ACD and COPR were available to participate in the assessment. To ensure that the Working Group would have a sufficiently broad range of scientific expertise, the Office of Science Policy solicited, from the NIH Institutes and Centers, nominations of basic and clinical scientists from their advisory councils to serve as ad hoc members. The NIH Director selected 6 ad hoc members with scientific expertise in areas not already represented by Working Group members, 4 of whom were available to participate. Dr. Ting-Kai Li of the ACD was selected by the NIH Director to chair the Working Group. The final Working Group consisted of 26 members: 6 ACD members, 16 COPR members, and 4 ad hoc scientists (see Table 1). This combination of individuals provided broad representation of the scientific and medical communities, health care providers, patients, and other representatives of the public. Moreover, it provided the expertise and perspectives necessary for evaluating the scientific quality and social relevance of the outcomes of the NIH Research Program.

Briefing Process

Working Group members (as well as all other COPR and ACD members who could not attend the meeting) were provided with comprehensive background materials on GPRA, the NIH Performance Plan, and the NIH GPRA assessment and reporting process. The backbone of the briefing material was a Q&A-style overview which addressed the GPRA; how the NIH is responding to the GPRA; the structure and content of the NIH GPRA Performance Plan; the need for an assessment of the Research Program outcomes; the Assessment Working Group; expectations for the Working Group; the assessment materials; and processes and activities before, during, and after the assessment meeting. Supplemental materials were provided as appropriate for each topic.

The briefing materials were followed up with a series of teleconferences with subsets of Working Group members to review the briefing materials; answer any questions about procedural issues, the nature of the assessment, and specific assignments; and to revise and reach consensus on the draft assessment criteria. The Working Group chair participated in these teleconferences.

Assessment Criteria

NIH provided the Working Group with a draft set of assessment criteria for their consideration. The draft criteria were discussed and modified significantly in the teleconferences led by the Chair of the Working Group. For example, the final criteria described two levels of goal achievement, rather than a single level; the wording of the first goal was modified; and an overarching point to consider was added as a preface to the criteria.
The final assessment criteria (Table 2) describe two levels of performance: having *successfully met* the goal and having *substantially exceeded* the goal. However, it was explicitly pointed out to the Working Group members, in a formal guidance document contained in the assessment materials notebook and later in an actual ballot, that a third level of performanceCnot having met the goalCwas also possible and could be considered.

The assessment criteria were modified and finalized by the Working Group and circulated to them before the actual assessment materials were sent out to the Working Group.

Assessment Materials

The assessment material was discussed and then prepared by the NIH Institutes and Centers (ICs), with guidance from the Office of Science Policy. The assessment material consisted of four types of narratives, that together provide an extensiveCbut by no means exhaustiveCillustration of NIH=s research outcomes that address the qualitative Research Program performance goals:

- *Science Advances* describe a specific scientific discovery published within the past year and supported by NIH funding, to place it in the larger context of what is known and unknown, and to describe the significance of the finding to science, health, and/or the economy. Science advances are one-page narratives that contain a descriptive title, a background section, a description of the advance, a discussion of the significance or implications of the advance, and citations of the scientific publications that support the advance. The actual published articles were not provided as part of the assessment materials, but were available upon request and at the Working Group meeting.

- *Science Capsules* provide a snapshot of the breadth and scope of NIH Research Program outcomes. There are obvious limitations to the sheer number of detailed, one-page science advances that the Working Group members could be expected to review and assimilate.

Science capsules are the ACliff notes@ version of science advances, consisting of a short paragraph that succinctly captures an advance and its significance, as well as citations.

- *Stories of Discovery* address the major limitation of traditional science advancesCthe fact that they address a single, incremental finding. Biomedical progress is usually achieved through long-range investments in research; advances usually occur slowly and incrementally, often build upon one another, and sometimes have applications to seemingly unrelated areas of medicine. Stories of discovery are 1-2 page narratives that focus on one topic. Each story traces the major developments in that area over several decades. Important connections between advances in science and improvements in the quality of life, health, and health care, as well as any resulting economic benefits are also highlighted.

- *Research Awards/honors* demonstrate outside evaluation and recognition of the value of NIH Research Program outcomes. The award write-ups are brief descriptions of national and international scientific awards/honors received by NIH scientists and grantees within FY99. The brief narratives identify the researcher(s) and the award, describe the work being honored, and the significance/purpose of the award.

Each IC was asked to provide 10-20 science advances, 10-20 science capsules, and 1-2 Stories of Discovery. The ICs were also asked to Acode@ the scientific narratives as to the primary and secondary GPRA goal that they address. The narratives were sorted among the five qualitative GPRA Research Program goals, and the awards/honors were placed in a separate section in the assessment notebook.

The result was a compilation of assessment material that spanned nearly 500 pages and included almost 600 advances, capsules, and stories of discovery. The assessment materials were provided to the Working Group (as well as all other COPR and ACD members) three weeks in advance of the October 22 assessment meeting to allow sufficient time for review.

Working Group Responsibilities and Tasks

Working Group members were responsible for reviewing the assessment material provided by NIH, evaluating it in terms of the final assessment criteria, and sharing their findings with the other members of the Working Group in a series of discussions during the October 22 assessment meeting.

Specifically, each member was tasked with reviewing a subset of the assessment materials: those for Goal A (Add to the Body of Knowledge), those for one additional goal (Instruments and Technologies, Prevention, Diagnosis, or Treatment), and the awards. The rationale for this assignment is discussed below. Members were, however, encouraged to have a working familiarity with all of the material so that they could participate in all discussions.

Working Group members were also asked by the Chair to identify, if possible, approximately five scientific discoveries from each assigned goal that were particularly noteworthy, and to come to the meeting prepared to discuss at least one of those outcomes, as well as to identify any findings they considered marginal.

›Trial Run= of the Assessment Exercise

In preparation for the October assessment meeting, the Office of Science Policy carried out a mock assessment exercise in the Summer, 1999. Approximately 180 science advances that had been previously submitted to the Office of Science Policy for the FY99 Congressional Justification were sorted under the qualitative GPRA performance goals. NIH staffCfrom the Office of Science Policy; and the IC Planning and Evaluation and Scientific Program communitiesCwere asked to review the mock assessment materials, apply an early draft version of the assessment criteria to the materials, and to identify the challenges and difficulties of the exercise. Feedback from the mock assessment exercise informed decisions about the types, format, and amount of assessment materials; the composition and assignments of the Working Group; and the structure of the assessment meeting.

In particular, NIH staff who participated in the mock GPRA assessment exercise found that the thorough review of the *entire* package of assessment materialsCand this was considerably smaller than what went to the Working GroupCwas a daunting/overwhelming assignment. In deference to this widespread observation, each member of the Working Group was assigned two goals for which they would be asked to do an in-depth review and be prepared to discuss their findings.

October 22, 1999 GPRA Assessment Meeting

The five qualitative GPRA Performance Goals for the NIH Research Program served as the framework for the discussion-based assessment (agenda at Table 3).

After a brief introduction, the Working Group discussed in plenary session the research outcomes provided for Goal A (Add to the body of knowledge about normal and abnormal biological functions and behavior) and how well they met the assessment criteria. There were several reasons for having the full Working Group participate in the discussion/assessment of performance goal A. First, this goal accounted for the lion=s share of the assessment material. Because it covered a very broad range of biomedical topics, it required extensive discussion and the full range of scientific expertise and public perspectives present embodied in the Working group. In addition, this goal, and the material provided for it, underpinned many of the other goalsCsuch as the development of new or improved treatments, diagnostics, and prevention strategiesCso it was important that all members be conversant with the material. Finally, the initial plenary discussion served as a working model for the subsequent break-out sessions.

Discussions/assessment of goals 2-5 were conducted in break-out groups, consisting of approximately 5-6 members. ALessons learned@ in the mock assessment exercise were the basis for this mechanism. Near the end of the day, the break-out groups reconvened for a plenary discussion of their findings and input from the other members of the Working Group.

Post-meeting Activities

To avoid the application or appearance of peer pressure, after the assessment meeting each Working Group member was asked, for any goals he or she had assessed, to formally indicate their judgment as to whether NIH successfully met the goal, substantially exceeded the goal, or failed to meet the goal.

A verbal report of the GPRA assessment process was presented by Dr. Ting-Kai Li to the full ACD on December 2, 1999. A number of ACD members, including those who did and did not participate in the assessment, commented on the exceptional quality and usefulness of the assessment materials and recommended broad distribution of the materials.

Finally, NIH staff worked with the Working Group to develop a written report of the assessment.

Report of the GPRA Assessment Working Group

As was the assessment meeting, the report of the GPRA Assessment Working Group is structured around the five qualitative performance goals. Each goal is addressed in a separate chapter. The goal-specific chapters include an overview of the range of research outcomes (science advances and capsules, stories of discovery) provided for a given goal, including a list of the titles of the outcomes; the assessment criteria applied by the Working Group; and a detailed presentation of the assessment discussion, including the findings of the Working Group and highlights of the research outcomes considered most noteworthy by Working Group members.

Readers will note two types of ›overlap‹ in the report, both intentional, but for different reasons:

- The overview of research outcomes in each chapter represents a non-selective description of the various outcomes provided to the Working Group. The subsequent section on the assessment findings, however, represents specific selections of research outcomes by the Working Group and thus, in a few instances, the same research outcome is mentioned in both the overview and in the discussion sections.

- A subset of the research outcomes were equally relevant to two goals. For example, one outcome described a new technology for delivering drugs to the central nervous system, and this new technology was used to administer an anti-cancer drug. This outcome speaks as well to the development of new technologies (Goal B) as it does to the development of new

treatments (Goal E). Thus it was included in the research outcomes for both goals. This kind of intentional overlap, however, was kept to a minimum.

Table 1
NIH GPRA Assessment Working Group of the Advisory Committee to the Director, NIH

October 22, 1999

Ting-Kai Li, M.D., Chair (ACD)
Indiana University School of Medicine
Indianapolis, IN

Michael Anderson, Ph.D. (COPR)
Oklahoma City, OK

William Brody, M.D., Ph.D. (ACD)
Johns Hopkins University
Baltimore, MD

Theodore Castele, M.D., FACR (COPR)
Fairview Park, OH

Constance Cepko, Ph.D. (Ad Hoc)
Harvard Medical School
Boston, MA

Robin Chin, R.Ph. (COPR)
CVS ProCare
Providence, RI

Mary desVignes-Kendrick, M.D., MPH (COPR)
Houston Department of Health and Human Services
Houston, TX

Melanie Dreher, Ph.D., R.N. (COPR)
University of Iowa
Iowa City, IA

Rebecca Eisenberg* (ACD)
Stanford Law School (for 1999-2000 only)
Stanford, CA
*permanent address
University of Michigan Law School
Ann Arbor, MI

Pam Fernandes (COPR)
Needham, MA

David Frohnmayer, J.D. (COPR)
University of Oregon
Eugene, OR

Jacqueline Jones, M.D. (Ad Hoc)
Cornell University Medical College
New York, NY

Vicki Kalabokes (COPR)
San Rafael, CA

Marc Kirschner, Ph.D. (ACD)
Harvard Medical School
Boston, MA

Barbara Lackritz (COPR)
St. Louis, MO

Joan Lancaster (COPR)
Johnson City, TN

Debra Lappin, Esq. (COPR)
Englewood, CO

Jane Menken, Ph.D. (ACD)
University of Colorado at Boulder
Boulder, CO

Isaac Montoya, Ph.D. (COPR)
Houston, TX

Rosemary Quigley (COPR)
Ann Arbor, MI

Eduardo Rios, Ph.D. (Ad Hoc)
Rush-Presbyterian-St. Luke Medical Center
Chicago, IL

Robert Roehr (COPR)
Washington, D.C.

Arthur Ullian (ACD)
National Council on Spinal Cord Injury
Boston, MA

Emil Unanue, M.D. (Ad Hoc)
Washington University School of Medicine
St. Louis, MO

Thomas Vaalburg (COPR)
Holland, MI

Douglas Yee (COPR)
Morgan Stanley Dean Witter
Honolulu, HI

Table 2

Final Criteria for GPRA Assessment of NIH Research Outcomes

Points to consider for ALL goals: Scientific advances are generally incremental, building upon previous discoveries. The importance of a particular discovery may not be apparent immediately; its significance and impact upon human health and quality of life may become evident only after years of continued research. The recognition of noteworthy accomplishments in this fiscal year acknowledges this important relationship to research discoveries in the past.

Goal A: Add to the body of knowledge about normal and abnormal biological functions and behavior.

The NIH biomedical research enterprise *has successfully met this goal* when its research yields new findings related to biological functions and behavior, and the new findings are published and/or disseminated.

The NIH biomedical research enterprise *has substantially exceeded this goal* when, in addition to fulfilling the above criteria, any of the following apply:

- $ discoveries result in significant new understanding of a particular biologic or behavioral process. Such new understanding may open up new avenues of research or be applicable to other disciplines, other areas of research, or other diseases.
- $ research yields answers to long-standing, important biological and behavioral questions, or provides novel investigative approaches for addressing such questions.
- $ genomic information about humans, model organisms, and/or disease-causing agents is translated into new understanding of the role of genes and/or the environment in human health, disease, and behavior.
- $ discoveries have potential for translation into new or improved technologies, diagnostics, treatments, and preventive strategies.

Goal B: Develop new or improved instruments and technologies for use in research and medicine.

The NIH biomedical research enterprise *has successfully met this goal* when its research yields new or improved instruments and technologies for use in research and medicine, and the instruments and technologies are published and/or disseminated or made available to appropriate populations.

The NIH biomedical research enterprise *has substantially exceeded this goal* when, in addition to fulfilling the above criteria, any of the following apply:

- $ instruments and technologies improve quality of life. This includes new or improved ways to ameliorate/manage symptoms, relieve suffering, and restore/increase physical function/activity.
- $ technical barriers are overcome so that investigations that were previously impossible are now possible.
- $ instruments and technologies enable novel approaches to answering important biological and behavioral questions.
- $ instruments and technologies are applicable to other disciplines, areas of research, or diseases.
- $ new/improved methods for generating, organizing, and disseminating genomic and other biological and behavioral information are developed.

Goal C: Develop new or improved approaches for preventing or delaying the onset or progression of disease and disability.

The NIH biomedical research enterprise ***has successfully met this goal*** when its research yields new or improved approaches for preventing or delaying the onset/progression of disease and disability, and the findings are published and/or disseminated.

The NIH biomedical research enterprise ***has substantially exceeded this goal*** when, in addition to fulfilling the above criteria, any of the following apply:

- findings demonstrate potential to lead/contribute to the development of preventive measures or strategies for delaying the onset/progression of disease and disability.
- research-based advances and public health campaigns result in broad health impactsCsuch as reductions in morbidity and mortality, changes in health-related behavior, amelioration of health disparities.
- prevention strategies are applicable to other disciplines, areas of research, or diseases and conditions.
- discoveries improve quality of life by preventing or delaying the onset/progression of symptoms, suffering, loss of function, and/or injury.

Goal D: Develop new or improved methods for diagnosing disease and disability.

The NIH biomedical research enterprise ***has successfully met this goal*** when its research yields new or improved methods for diagnosing disease and disability, and the methods are published and/or disseminated or made available to appropriate populations.

The NIH biomedical research enterprise ***has substantially exceeded this goal*** when, in addition to fulfilling the above criteria, any of the following apply:

- new findings demonstrate potential to lead/contribute to the development of new and improved diagnostics.
- diagnostics improve health care and/or quality of life. This includes new or improved diagnostic methods that are more sensitive and accurate; allow diagnosis or detection at an early/earlier stage; enable early/earlier treatment or preventive interventions; predict future susceptibility to disease/disability; and/or are less invasive, painful, and/or costly than current techniques.
- diagnostic methods are applicable to other disciplines, areas of research, or diseases.

Goal E: Develop new or improved approaches for treating disease and disability.

The NIH biomedical research enterprise ***has successfully met this goal*** when its research yields new or improved approaches for treating disease and disability, findings are published and/or disseminated.

The NIH biomedical research enterprise ***has substantially exceeded this goal*** when, in addition to fulfilling the above criteria, any of the following apply:

- new findings demonstrate potential to lead/contribute to the development of new and improved treatments.
- new or improved treatments improve health care and/or quality of life. This includes treatments that are more effective or have fewer side effects; relieve suffering; are more cost-effective; are less invasive, painful, and/or costly than current methods; effect a cure or remission of disease; and/or restore/increase physical function/activity.
- treatment approaches are applicable to other disciplines, areas of research, or diseases.

Revisions per:

Teleconference with Working Group Chair and other ACD members	(9/16/99)
Discussion with Working Group Chair	(9/20/99)
Teleconference with Working Group Chair and COPR member	(9/22/99)
Teleconference with Working Group Chair and COPR members	(9/27/99)
Teleconferences with COPR and ad hoc members	(9/30/99)
Faxed communication with ACD members	(9/30/99)

Table 3

Meeting Agenda
GPRA Assessment of NIH Research Program Outcomes
October 22, 1999

10:00	Opening Remarks Introductions	Ruth Kirschstein, M.D. Working Group Members
10:20	Overview of GPRA	Lana Skirboll, Ph.D.
10:30	Plenary Session: Goal A (Add to the Body of Knowledge)	Ting-Kai Li, M.D. Melanie Dreher, Ph.D.
12:15	CLunch: On Your OwnC	
1:15	Concurrent Breakout Sessions: Goals B-E	
	Goal B: (Instruments and Technologies)	Eduardo Rios, Ph.D. Thomas Vaalburg
	Goal C: (Prevention)	Jane Menken, Ph.D. Mary desVignes-Kendrick, M.D.
	Goal D: (Diagnosis)	Ting-Kai Li, M.D.
	Goal E: (Treatment)	Arthur Ullian Isaac Montoya, Ph.D.
2:30	Break	
2:45	Plenary Discussion of Results from Breakout Sessions	
4:15	Adjourn	

CHAPTER 2

Goal A: Add to the Body of Knowledge about Normal and Abnormal Biological Functions and Behavior

Introduction

Much of health care today still involves treating the symptoms of disease without understanding its underlying causes and the precise mechanisms by which disease develops (pathogenesis). In order to effectively and systematically attack the diseases of today such as cancer, heart disease, AIDS, arthritis, diabetes, and addiction, we need a broad base of knowledge about normal living systems. We need to understand how living systems operate at both a Amicro@ levelCthe structure and function of genes, proteins, carbohydrates, and fatsCand at more Amacro@ levels, that is, how these molecules organize and function together as living units (cells, tissues, organs, whole organisms, and even communities). As important, we need to understand how disease, genetic alterations, and environmental factors affect the function of these molecules, cells, tissues, organs, and organisms, and their consequences for human health.

All organisms are made of the same basic materials, and many share similar genetics and physiologic processes, so researchers seeking to understand both normal and disease processes in humans can learn a great deal by studying similar systems in simpler Amodel organisms@ like bacteria, slime molds, yeast, fruit flies, zebrafish, and rodents. Model systems have proven to be essential tools for understanding a wide array of human conditions, providing critical new insights into mechanisms associated with cardiovascular, gastrointestinal, neurological, structural, and other defects that may have counterparts in human disorders. Animal models can be used for studying the physiological course of a disease, determining the identity and function of the genes and proteins involved in health and human disease, testing new treatments, and developing and testing methods for preventing disease and disability.

At first glance, this goal may appear to focus on laboratory research, but it actually encompasses clinical research as well. The aim is to be able to put all the parts together to understand normal biological activities and how they malfunction in disease and disability. This, in turn, will provide the fundamental theories and concepts for more disease-oriented investigations that lead to new methods for diagnosing, treating, and preventing disease and disability. It may take years, however, after a new discovery is made for the potential health applications to become clear. Thus, just as no one can predict what researchers will discover in the future, neither can the

eventual clinical applications of today's laboratory results be known. As productive as the past has been, the future promises to be still more exciting as researchers gain an even greater understanding of living systems and apply that understanding to questions of health and disease.

Overview of the NIH Research Outcomes Provided for Goal A

The NIH Institutes and Centers submitted 265 science advances, science capsules, and stories of discovery that, in their judgment, demonstrated the acquisition of new knowledge about normal and abnormal biological functions and behavior (see Table 4).

Many of the discoveries within Goal A were at the level of the gene, including the identification and isolation of new genes (from both humans and model organisms) and new understanding about how genes function. New, detailed genetic and physical maps of the human genome, as well as new and improved sequencing technologies arising from the Human Genome Project have reduced the time it takes to find a disease gene from years, to months, to weeks, to sometimes just days. This was reflected in the research outcomes, which included the identification of a number of new genes, including those involved in response to anesthesia, bacterial infections and certain inflammatory diseases, type 2 diabetes, narcolepsy, retinitis pigmentosa, learning behaviors, early onset dementia, epilepsy, osteoporosis, and certain cancers and leukemias. Findings such as these are important, because once a disease gene is identified, the next step is to determine the role it plays in human health and disease. With information from the Human Genome Project and other genomic endeavors, researchers can make these critical links rapidly, yielding a comprehensive picture of how our genes provide the instructions for the fundamental processes of life and laying the groundwork for the development of new and more effective diagnostics, treatments, and preventive strategies.

A number of the outcomes represented new understanding of the complexities of gene expression and of the basic cellular functions underlying human development. For example, a number of NIH-supported researchers discerned how small signaling molecules function in controlling normal cellular processes such as cell growth and metabolism. Others discovered a bile acid signaling pathway that may regulate cholesterol balance.

Other findings delineated the function of specific genes. The genetic basis of cancer has been a prime target of investigation in recent years, with many studies focused on the identification of chromosomal and gene alterations that play a role in the development of cancers. For example, previous research efforts resulted in the identification of mutations in the BRCA1 gene which account for a large percentage of inherited breast cancers and also confer an increased risk of ovarian and prostatic cancers. In the past year, NIH-supported research extended these findings by determining the normal biological role of BRCA1, how alterations in the gene act to increase cancer risk, and that the *p53* gene (a tumor suppressor gene) is involved in BRCA1-associated tumor formation. Other research outcomes significantly increased our understanding of how a

recently discovered tumor suppressor gene known as PTEN functions normally and how mutations in the gene can allow tumor cell invasion and bypass of a programmed cell death mechanism. Findings such as these are beginning to define the exact symphony of cell signals involved in developing and suppressing cancers. Detailed knowledge of how tumor suppressors function and malfunction could lead to the development of drugs that suppress cancer progression. For example, drug development could be targeted at finding agents that mimic normal PTEN actions to suppress cancer progression.

Discoveries at the chromosomal level have raised new prospects for identifying genes that might be critical in the development of prostate cancer. For example, NIH-supported researchers identified a region of deletion on chromosome 8 that existed in 80 percent of prostate tumors studied. Deletions in this same region of chromosome 8 were also observed in 63 percent of precancerous prostate lesions, suggesting that abnormalities in these chromosomal region may be associated with early stages of prostate cancer development. Interestingly, this region overlaps with a portion of chromosome 8 thought to play a role in hereditary breast cancer. Further analysis of the genes in this region could yield critical new insights into the development of prostate and breast cancers.

Goal A genetic discoveries were by no means confined to cancer. Scientists seeking to better understand the genetic basis of osteoporosis (which can run in families) found that osteoporotic hip and wrist fractures may be partially rooted in a gene on chromosome 19, the apolipoprotein E gene. Women over age 65 with the E*4 Aversion@ of this gene were determined to have twice the risk of hip and wrist fracture. Intriguingly, the APOE*4 gene has been previously shown to be associated with late-onset forms of Alzheimer=s disease and with osteoporosis in patients on dialysis. So how could one gene play a role in two such seemingly disparate disorders? The new findings have led scientists to speculate on this: individuals with the APOE*4 gene may have reduced levels of vitamin K, which stimulates bone formation and reduces bone-cell loss; people with Alzheimer=s disease have a higher risk of hip fracture, and the APOE*4 gene has now been found to have connections to both; and women with the APOE*4 gene experience greater weight loss than those who have a different version of the APOE gene, and weight loss contributes to bone loss, which in turn could affect fracture risk.

A number of research discoveries involved genes that play a role in diabetes. For example, major progress was achieved toward identifying genes important for islet cell development. Pancreatic islet cells secrete proteins, such as insulin, that regulate sugar levels in the body. Investigators discovered that the *BETA2* gene is important in regulating insulin and that mutation in this gene disrupts proper islet cell formation. They also isolated a protein from pancreas cells which regulates the activity of *BETA2* in the early stages of pancreas development. Knowledge of the relationship of pancreatic genes and their regulators will lead to a better understanding of the molecular mechanisms controlling endocrine pancreas formation and could lead to new therapies for diabetes. Another outcome described new insights into how type 2 diabetes develops and

progresses. New findings suggest a unifying hypothesis for type 2 diabetes in which insulin resistance in all insulin-responsive cells could result in the classical manifestation of type 2 diabetes. In humans, combinations of environmental and genetic alterations in the insulin receptor and in the insulin signaling pathway could provide a mechanism for the development of type 2 diabetes. Increased understanding of these events has implications for new approaches to treatment and prevention.

Progress in mapping the human genome has been complemented by important genomic studies in other animals and in microbes that infect and cause disease in humans. The same technologies that allow us to map and sequence human genes have proven to be essential in mapping and sequencing the genomes of infectious agents. This approach can lead to the advancement of vaccine development and the discovery of drugs targeted at specific pathogens. For example, NIH-supported researchers identified two specific regions of the genome of the hepatitis C virusCa common cause of chronic liver disease and liver cancerCthat are necessary for the virus to infect cells and cause disease. This new knowledge could lead to the development of novel preventive agents to halt the spread of this infectious disease. Similarly, another outcome highlighted completion of the sequencing of the genome of the bacterium *Chlamydia trachomatis*. Chlamydia genital tract infections are one of the most common infectious diseases reported to the Centers for Disease Control and Prevention and can lead to pelvic inflammatory disease, ectopic pregnancy, chronic pelvic pain, infant pneumonia, and increased risk for HIV infection. A combination of biochemical and computer studies has identified unique essential proteins and pathways that can provide targets for the development of novel therapeutics, vaccines, and diagnostics.

Some Goal A outcomes featured zebrafish (*Danio rerio*) as a valuable model for advancing understanding of human genes, development, and disease. Zebrafish genome studies are providing clues to how genetic mutations can trigger disease, largely because many of the key proteins and developmental and cellular processes are conserved across life forms. Mutation screening studies in the zebrafish have proven to be a good approach to finding human disease genes. For example, researchers identified a zebrafish gene that causes anemia and found that it was the equivalent of a defective human gene that causes congenital sideroblastic anemia. This represents the first animal model for study of this human anemia. Another zebrafish mutant was identified with a form of porphyria, which in human creates disabling photosensitivity. Thus, research on mutant fish may help to identify new therapies for patients with these disorders. The NIH has supported the Zebrafish Genome Initiative since 1998 and is currently supporting the establishment of a zebrafish stock center. Plans are underway for the expansion of an integrated informatics system for zebrafish genes and mutants that can be interfaced with other genome databases.

Genes provide the instructions for making proteinsCmolecules made up of a number of amino acids arranged in a specific order determined by the genetic code. Proteins are intensely studied

because they are involved in nearly every biological function. Proteins include the enzymes that act as catalysts for many of the chemical reactions necessary to life and many of the hormones that regulate growth and development. Proteins are also important components of the cell=s physical structure, making up half of the cell=s dry weight. They help transmit messages from nerve cells; work in muscle cells to convert chemical energy, which permits movement; and in the cell membrane, control molecules entering and leaving the cell. As such, the study of proteins is a crucial step in understanding human health as well as the initiation and progression of disease.

A number of research outcomes described important new understanding of the role of proteins and vitamins in human health and disease. For example, folic acidCa B vitamin that protects against certain birth defects as well as heart attacks and strokesCwas discovered to speed up the conversion of a potentially harmful compound called homocysteine into a harmless amino acid needed to fuel chemical reactions in the body. Scientists figured out that folic acid works by improving the fit between an enzyme and a helper molecule that work together to break down homocysteine. Researchers also discovered an enzyme, dubbed Pin1, that seems to be able to untangle the knots of Atau@ proteins that are a hallmark of Alzheimer=s disease and are believed to cripple normal communication among brain cells. The Arehabilitated@ tau proteins can then perform their normal cellular functionCassembling and maintaining a scaffolding that stretches the length of nerve cells and is used to ferry nutrients and structural components throughout the cell. The discovery of the healing power of Pin1 in nerve tissue may aid efforts to find new therapies to treat Alzheimer's disease and other neurodegenerative diseases that disable the brain. Another research outcome adds to our understanding of how neurons in the adult brain are maintained and actually replaced, a surprising finding given that it was traditionally believed that the number of brain cells was established at birth only to decrease in number throughout the life span. Scientists found that a protein in the body, basic fibroblast growth factor, is transported across the blood-brain barrier into the brain, where it stimulates nerve cell growth, and this process occurs during development as well as in adulthood. These findings have exciting implications for developing treatments for brain damage associated with neurodegenerative, congenital, and traumatic brain disorders.

A number of outcomes highlighted how new knowledge of the identity, structure, and function of the proteins and molecular pathways of disease-causing microbes can suggest new strategies for stopping the replication of infectious agents. For example, studies of the structure of the active form of reverse transcriptaseCan enzyme of the human immunodeficiency virus (HIV) that causes AIDSCrevealed how HIV becomes resistant to AZT-like drugs and provides detailed insight into how to develop better anti-AIDS drugs. Investigators also discovered a new mechanism for how the hepatitis C virus (HCV)Cwhich causes chronic liver diseaseCresists the antiviral effects of interferon, the principal treatment for chronic HCV infection. Understanding the ways in which a virus evades a host=s natural defenses should provide new insights into

designing therapies that attack the virus at unique molecular pathways and cause fewer side effects.

Another important discovery highlighted for Goal A described how investigators isolated a protein called anophelin from the saliva of the mosquito that transmits the malaria parasite. Anophelin works by inhibiting blood clotting, which not only enhances the mosquito=s ability to get its blood meal, but also facilitates the transmission of parasites carried by the mosquito. This new knowledge not only suggests new treatment and prevention modalitiesCsuch as vaccines designed to interact with anophelin and thus diminish parasite transmissionCbut also could lead to development of a new class of anticoagulants.

Mycobacterium tuberculosis, the cause of tuberculosis, is the leading cause of bacterial infection and death worldwide. Combating ***M. tuberculosis*** presents a challenge due to its ability to thrive both outside and inside host cells. In an important advance, scientists defined a pathway by which certain cytotoxic (cell-killing) T lymphocytes release a bacteria-killing protein, called granulysin, and a protein that clears the way for it, that disrupts ***M. tuberculosis*** within the cells. This finding has important implications for vaccine research.

Middle ear infection, or otitis media, is one of the most significant health problems for children in the United States. NIH-supported investigators continue to focus on the identification of specific molecular mechanisms by which bacterial and viral infections cause otitis media. A recent set of studies yielded new understanding of the steps that lead to otitis media, information critical for the development of clinical interventions such as vaccines.

Clearly, understanding the fundamental aspects of protein regulation and function can lead to new therapies for disease, and not just infectious disease. Obesity, a major cause of morbidity and mortality in the United States, provides an example. Previous research had revealed that leptin, the protein product of an obesity gene, is secreted by fat tissues. A Goal A outcome described a recent discovery that leptin and other hormones (such as melanocyte stimulating hormone) act on a region of the brain called the hypothalamus to suppress appetite. This new information on pathways that control food intake has led to fundamental advances in our understanding of body weight regulation and has implications for the development of therapies to treat obesity. Other research outcomes described new insights into the fundamental roles of proteins in disease progression in multiple sclerosis, type 2 diabetes, glaucoma, and cataracts.

Another major category of research findings were at the level of the cellCa biologically larger and more complex unit than DNA or a gene. All cellsCwhether from a bacterium, plant, mouse, or humanCare made of the same basic materials: nucleic acids, proteins, carbohydrates, water, fats, and salts. For this reason, scientists seeking to understand both normal and disease processes in humans can learn a great deal by studying similar systems in Amodel organisms@ like worms, yeast, rodents, and fruit flies.

For example, one of the most exciting breakthroughs to occur in cell biology in recent years came about through the use of animal models and limited human studies. Scientists were finally successful in isolating, and then growing in the laboratory, specialized cells known as stem cells. Stem cells have the ability to divide for indefinite periods in culture and to give rise to specialized cells. Many kinds of stem cells are found in the human body, with some more differentiated, or committed, to a particular function than others. In other words, some stem cells are capable of giving rise to most all or most of the tissues of an organism. Others are only able to give rise to cells that have a particular function (e.g., blood stem cells which give rise to red blood cells, white blood cells, and platelets; and skin stem cells that give rise to the various types of skin cells), and they serve to renew tissue throughout an individual=s life.

Finding out just how stem cells function and can be regulated will bring biomedical research to the edge of a new frontier. Some Goal A outcomes highlighted important first steps toward unraveling some of these secrets. For example, scientists discovered a class of related proteins in animal cells that commit embryonic precursor cells to mature into liver cells. Another group of advances documented that researchers are closer than ever before to human clinical trials to repair skeletal defects. The research used a type of stem cell called bone marrow stromal cells, which have the ability to form bone, cartilage, and other connective tissues. By growing and treating the stromal cells in tissue culture before transplanting them, researchers successfully generated new bone in the skulls of mice. Several other advances were made in animal models of neurological diseases. These furnished the first evidence that stem cells from the brains of mice can repair damage from brain disorders in which the degeneration or dysfunction is Aglobal,@ rather than in discrete locations. Before stem cells can be used therapeutically, however, the factors that influence their growth and specialization must be thoroughly understood. In addition, research in animal models must be tested in human cells, and safe methods must be devised to obtain stem cells from adults.

Other methods which offer hope for replacing lost or damaged brain cells were also featured in the research outcomes of Goal A. For example, scientists studied a part of the brain known as the hippocampus, an area associated with learning and memory. After they Atagged@ the cells of the hippocampus in rats and subjected the animals to a rigorous training period, a dramatic increase in the number of neurons in the hippocampus was observed, suggesting that brains need constant challenges to create new cells throughout a lifetime. Related results shed new light on how the brain changes during the acquisition of memory, that is, how synaptic transmission can become strengthened with repeated use. These studies demonstrated that subtle alterations in the cellular and molecular mechanisms underlying synaptic change during development and adulthood might lead to devastating brain disorders, such as schizophrenia.

Other discoveries at the cellular level have provided important insight into how potassium ions flow from cell to cell, through channels that open and close in response to biochemical stimuli. Using a technique called X-ray crystallography, scientists were able to determine a part of a

specialized potassium channel that helps regulate heart rhythm. Defective versions of this channel underlie one form of a serious genetic heart condition that causes irregular heartbeat and sudden death. In related findings, scientists learned that the two genes that are affected in a form of epilepsy code for subunits that together make up an ion channel called the AM channel,@ which allows potassium to enter and leave cells. The M channel is an important regulator of electrical activity in nerve cells. These results provide an answer to what causes a particular form of epilepsy and could provide a target for developing more specific drugs to treat the disorder.

Febrile (fever-related) seizures are a common childhood occurrence that can be not only frightening, but often lead to emergency room visits and hospitalization. One important question is whether there are long-term effects from the seizures. A relevant research outcome arose from studies of prolonged seizures in rat pups. Investigators found long-lasting changes in the electrical activity of specific types of nerve cells in the hippocampus, an area of the brain critical in epilepsy. Investigators are now studying how the brain responds to this change in nerve cell function and whether their findings apply to humans. They believe that febrile seizures change the way some brain cells function, which may decrease the protection the brain normally has against seizures.

Understanding how cancerous cells develop and how they override the normal mechanisms that control cellular proliferation and division has eluded scientists for many years. Until now, no one has been able to identify the minimum number of defined genetic events needed to transform a normal human cell into one that will continue to proliferate indefinitely. In a striking achievement, a team of NIH-supported scientists converted normal human cells to tumor cells in a culture dish by altering the expression of a defined set of genes. The ability to introduce specific genetic alterations to transform cells provides the exciting opportunity to define the biochemical pathways in a cell that must be disrupted in the development of cancer. This could lead to the discovery of treatments that target specific steps in cancer development. Related studies that focus on the natural death of cells (apoptosis) are likely to contribute additional information to how one might promote cell death in malignant tumors and other disorders.

Findings at the molecular and cellular level are providing more in-depth understanding of how disease progresses in complex systems such as the brain, the cardiovascular system, and the skeleton. While it has long been suspected that diet plays a crucial role in the development of heart disease, it has only been recently that scientists have been able to understand exactly what role certain dietary elements play. For example, results described within Goal A suggest that fish oil, consisting of a certain type of polyunsaturated acids, reduces the incidence of life threatening heart arrhythmias that can cause sudden cardiac death. These important fatty acids directly affect cardiac electrical activity.

Other outcomes addressed atherosclerosis, in which coronary arteries and other blood vessels become obstructed by deposits of plaque (masses containing cholesterol and other lipid

substances). Previous atherosclerosis research focused on developing ways to promote angiogenesis (growth of new blood vessels) in order to circumvent obstruction of coronary arteries. An outcome described for this goal, however, showed that development of plaques may be associated with the formation of new blood vessels, so blood vessel growth must be *inhibited*, not promoted, to prevent atherosclerosis. This surprising turn of events has refocused efforts on finding ways to slow the growth of new blood vessels and thereby prevent atherosclerosis. Other scientists determined that infection with the respiratory pathogen known as *Chlamydia pneumoniae* can contribute to the development of atherosclerosis.

It has been observed for some time that coronary heart disease develops about 10 years later in women than in men, and the loss of estrogen production following menopause is believed to be a contributing factor. Estrogen is thought to exert a beneficial influence on a woman=s cholesterol profile. A research outcome described an important study which confirmed that the addition of estrogen replacement therapy to a cholesterol-lowering drug regimen in postmenopausal women improved their cholesterol profiles to a greater degree than either therapy alone. Estrogen also appears to play an important role in the functioning of another system, the central nervous systemCthe brain in particular. In a groundbreaking study, investigators used sophisticated imaging technology to show that estrogen alters brain activation patterns in postmenopausal women as they perform memory tasks. The results showed that it is possible to alter brain organization in older individuals, indicating that the memory systems of mature women are responsive to external stimuli rather than being fixed or immutable.

Other outcomes addressed the effect of external stimuli on the brain. For example, researchers found that new mothers suffering from depression use different speech patterns and tones than do non-depressed mothers, and the pitch and tones in a depressed mother=s voice do *not* promote attention or learning in a baby. Other studies revealed that babies who experience early difficulties in learning often have later problems with behavior and school performance. These findings underscore the importance of recognizing and treating post-partum depression and of developing interventions for children with depressed mothers.

In another research outcome relevant to better understanding of the brain, investigators analyzed changes in brain structure that occurred during the maturation of both healthy children and those with childhood-onset schizophrenia. They observed definite abnormalities in the brains of children with schizophrenia, such as increases in volume in some areas and decreases in others, especially in regions critical for memory and planning. It is likely that these progressive changes in the brains of children with schizophrenia are related to triggering, or actual onset, of the illness.

One outcome from population-based studies described how in childhood and early adulthood, economic resources have a significant impact on health outcomes, because this is the time that health levels and trajectories are being established. At older ages, however, health events have

economic implications that go well beyond direct medical expenses. Other outcomes addressed gender and other differences in disease morbidity and mortality. For example, although overall deaths from heart disease have fallen dramatically in the United States, the decline has not been as dramatic for diabetic individuals. And, although the rate of heart disease dropped in diabetic men during 1971-1993, it actually rose by 23 percent in diabetic women. Research on the reasons for these discrepancies is essential, particularly because it is likely to show the importance of differential approaches to prevention and treatment among these various populations.

Other outcomes from population-based studies were relevant to substance abuse and addiction health services. NIH-supported researchers compared health plans that placed no limits on substance abuse treatment utilization to those with annual limits on such treatment. They found that removing annual limits on substance abuse treatment had only a small absolute effect on overall insurance costs under managed care. These results suggest that substance abuse benefits under managed care can be offered on an as-needed basis with little effect on costs to members, but with significant benefit to the recipients and potentially to employers.

Determining the possible adverse effects of environmental agents on a population often entails large-scale, long-term studies. Such studies have previously documented that occupational exposure to the dust of the major grains cultivated in the West (e.g., sorghum and barley) cause a variety of respiratory conditions, including asthma, bronchitis, and Agrain fever.@ An important Goal A outcome documented similar adverse respiratory health effects of occupational exposure to rice dust in China. Little attention had previously been paid to this, but rice is a major grain staple in China and a large number of farmers and grain handlers are exposed. This finding could lead to strategies for preventing chronic lung illnesses and avoiding major health care expenditures.

Table 4
Titles of NIH Research Outcomes Provided for Goal A
(Add to the Body of Knowledge about Normal and Abnormal Biological Functions and Behavior)

SCIENCE ADVANCES

$ Basic Research Shows How Folic Acid Protects Against Heart Disease and Birth Defects
$ Enzyme Can Repair Alzheimer's Tangles
$ Scientists Discover How Immature Cells Decide to Become a Liver
$ AIDS Enzyme Caught in the Act
$ Heavy Metal Research is Music to Biologists' Ears
$ Gene Involved in Anesthesia Response Identified
$ Fruit Fly Research Links Cocaine Sensitization With Biological Clocks
$ Potassium Channel Research May Shed Light on Heart Ailment
$ Inhibiting New Blood Vessel Growth Reduces Atherosclerotic Plaque in Mice
$ Combination of Therapies May Reduce Risk of Coronary Heart Disease in Women
$ Diet High in Fatty Fish May Protect Against Sudden Cardiac Death
$ New Understanding of Increased Risk of Blood Clots in Old Age
$ Insight into How Hepatitis C Virus Evades Host Defenses May Lead to New Therapies
$ Molecular Basis for Malaria Resistance and Susceptibility in Pregnant Women Defined
$ Latent Infection of CD4+ T Cells Provides a Mechanism for Lifelong Persistence of HIV-1
$ Molecular Studies of Hepatitis C Virus Identify Sequences that May Be Targets for Preventive Agents
$ Maternal HIV Blood Levels Are Strong Predictors for Risk of Perinatal Transmission
$ Identification of Salivary Anti-Thrombin from the Anopheles Mosquito May Lead to the Development of Novel Malaria Pharmaceuticals
$ Knowledge about an Immune Cell Receptor Type Provides Clues about Immunoregulatory Processes that Affect Pregnancy
$ Natural Model of Cutaneous Leishmaniasis Provides Insights into Vector=s Role in Pathogenesis and Potential for Novel Prevention Strategies
$ Sequencing of Organism involved in Sexually Transmitted Diseases and Blindness Provides Clues for Vaccine and Drug Development
$ Preventing Unwanted T Cell Activation by Triggering CTLA-4, A Negative-Signaling Molecule
$ The Adult Thymus Is Capable of Rebuilding the Immune System after Treatment of HIV Infection
$ Insulin Resistance in Tissues Underlies Type 2 Diabetes
$ Diabetic Heart Disease Still a Disproportionate Problem
$ Increased Insulin Sensitivity and Obesity Resistance in Mice
$ Types of Pituitary Gland Cells: How Are They Determined?
$ Understanding the Regulation of Gene Expression
$ Pathways In the Brain That Control Food Intake

Science Advances, continued
$ Paracellin-1, a Renal Protein, is Required for Magnesium Homeostasis
$ New Mechanisms of Resistance to Urinary Tract Infection are Identified
$ Turning Brain into Blood //Turning Bone Marrow into Liver Cells
$ Mechanisms of Female Sex Determination and Development
$ New Therapeutic Approach for Inborn Metabolic Errors
$ The Role of Breast Cancer Gene (BRCA1) Mutation in the Development of Breast Cancer
$ Regulation of Genetic Expression During Blood Formation
$ Proteins as Genetic Material in Human Disease
$ Progress in Zebrafish Research
$ Adolescents May Be Vulnerable to Some Types of Alcohol-Induced Memory Impairment
$ Appetite-Regulating Protein Implicated in Alcohol Consumption
$ Scientists Discover Gene Mutations Defining New Group of Inflammatory Diseases
$ Inbred Mouse Strains Yield Clues to the Genetics of Bone Density
$ Febrile Seizures Modify Brain Excitability
$ Chemokines and Multiple Sclerosis
$ Gene for Narcolepsy Discovered
$ Understanding the Potential of Neural Stem Cells
$ Understanding a Retinal Degenerative Disease
$ Retina-specific Gene Causes Autosomal Dominant Retinitis Pigmentosa
$ New Clues to How the Lens Forms and Maintains Its Structure
$ New Findings Link Nitric Oxide to Nerve Cell Damage in Glaucoma
$ Growth Factor Research May Lead to New Treatments
$ Identification of Modified Forms of αB-Crystallin in Human Cataracts
$ The Dual Role of Interleukin-12 in Regulation of Autoimmune Retinal Disease
$ Interferon-γ Increases the Severity of Uveitis and Induces Retinal Degenerative Changes in Transgenic Rats
$ Hair Cell Differentiation and Specification
$ A Novel Calcium Response in Hair Cells
$ Identification of Molecular Mechanisms of Pathogenesis of Otitis Media
$ The Vestibular System Influences Cardiovascular Control in Humans
$ Taste Receptors
$ Deciphering the Code for Odors
$ Pheromone Pathways of the Brain
$ Preventing Early Miscarriage
$ Improving Treatment for Polycystic Ovary Syndrome
$ Protein Has Potential to Treat Brain Damage
$ Islet-Specific Transcription Factors and Development of the Endocrine Pancreas
$ Effects of Estrogen on the Brain After Menopause
$ Identifying a Risk Factor for a Common Birth Defect
$ AKiller Cells@ and Resistance to Cancer Metastasis
$ Gender Differences in Heart Muscle Function

Science Advances, continued

$ Complement System May Be Useful Target for the Treatment of Sepsis
$ Substance Abuse Treatment Can Be Cost-effective
$ Chemical Identified That Can Block Brain Damage Caused By Methamphetamine
$ A Chemical Produced in the Brain May Offer New Insights into Tourette=s Syndrome and Parkinson=s Disease
$ Chronic Marijuana Smokers May Undergo Withdrawal When They Quit
$ Dopamine: More than Just the Pleasure Molecule
$ Creating Human Cancer Cells
$ Published Research Using Linked SEER-Medicare Data
$ Interpretation of Emerging Patterns and Trends in Cancer
$ Health Effects of Cigar Smoking
$ Gene For Making Mice Smarter Offers Clue To Human Intelligence
$ New Brain Cells Formed In Response To Learning
$ How the Brain Pays Attention
$ Clues to How our Brains Organize Visual Perceptions
$ Newly Identified Protein Essential For Message Transmission In The Brain
$ Clues to the Nature of Schizophrenia
$ Learning How We Learn
$ Neural Activity Shapes the Brain=s Cells
$ New Players in the Molecular Basis of Memory and Learning
$ Depressed Mothers= Speech Affects Learning In Babies
$ Link Established Between Cessation of Cell Divisions and the Mammalian Aging Process
$ Caloric Restriction Slows the Aging Process
$ Gene Therapy Can Maintain Muscle Mass and Strength
$ Does the Relationship between Health and Economic Status Reverse Over the Life Course?
$ Protein Complexes in Cells Can Use Energy to Promote Subsequent Function or Loss of Function
$ Control of Programmed Cell Death in Human Tumor and Immune Cells
$ Gene on Chromosome 13 Linked to a Form of Familial Early-Onset Dementia
$ Two Amino Acid Residues are Critical to Presenilin Protein Activity: Leads to Potential Targets for Treatment of Early-Onset Alzheimer=s Disease
$ New Neurons Are Produced in the Adult Human Brain
$ Age Does Not Change the Ticking of the Circadian Clock, but it=s Faster than We Thought
$ Synchrotron Resources Enable Landmark Studies of Ribosome Structure
$ HIV Infection Persists Even With Combination Drug Therapy
$ Nuclear Magnetic Resonance Reveals More Pieces of the Prion Puzzle
$ AIDS Virus Strains in Africa: Novel and More Virulent
$ Cooking Fuel, Indoor Pollution, and Tuberculosis in India
$ Lung Disease in Rice Granary Workers
$ Nitric Oxide Perfusion in Patients with Sickle Cell Disease
$ Evidence that Alcohol Has ADocking Sites@ on Cells Raises Potential for New Medications

Science Advances, continued

$ Alcohol Consumption Influenced by Different Genes in Females and Males, Suggesting that They May Process Alcohol Differently
$ Gene Therapy Restores Muscle in Aging Mice
$ Skeletal Muscle Damage Induces Heart Disease
$ Tumor Necrosis Factor Mediates Orthopaedic Implant Osteolysis
$ Molecular Basis of the Physical Connection Between Epidermis and Dermis
$ Hair: Molecular Biology, Embryology, Cycling, and Diseases
$ Newly Discovered Genes May Contribute to Epilepsy
$ Growth Factors Prevent Loss of Embryonic Nerve Cells Exposed to Toxins in Test Tube
$ Violence Reduction Sustained After Alcoholics Receive Behavioral Marital Therapy
$ Light-to-Moderate Drinkers Account for More On-the-Job Problems than Do Heavy Drinkers
$ One In Four U.S. Children Exposed to Alcohol Abuse or Alcoholism in Family
$ Does Moderate Alcohol Intake Protect the Heart? Scientists Track Pathways that Could Lead to Cardioprotection
$ Steroid-Induced Bone Loss: Mouse Findings Point to Preventive Possibilities
$ Risk of Hip and Wrist Fractures Shown Linked to Chromosome 19 Gene
$ Physical Activity and Osteoarthritis
$ Restoring Production of Brain Cells in Old Age
$ Killing of Intracellular *Mycobacterium tuberculosis* by an Antimicrobial Protein Found in Human Cytotoxic T Lymphocytes
$ Ancient Receptors Trigger Inborn Reactions to Bacteria
$ Vigorous Cytotoxic Response Leads Recovery against Hepatitis C Virus
$ The Mammalian Gene Collection: A Resource for Studying Gene Expression and Function
$ Genetic Defect in Myeloid Leukemia Explained
$ Absence of Linkage between Bone Formation and Bone Loss
$ Mechanism of Fungal Adhesion Identified
$ Why Prostate Cancer Homes to Bone
$ Major New Tumor Suppressor Provides Fresh Insights into Cancer
$ Secretory Leukocyte Protease Inhibitor (SLPI) Inhibits Arthritis
$ Acceleration of Wound Healing in Aged Humans
$ Breast Cancer, Heart Disease, Osteoporosis, and the βERKO Mouse
$ A Common Link in Failed Pregnancies
$ Breast Cancer Susceptibility Gene, BRCA1 - How Does It Work?
$ Inhibitors of Growth Factors Inhibit Pulmonary Fibrosis
$ Subtle Mutations Can Have Disastrous Effects When Combined
$ Signaling Environmental Stress C How Do Cells Respond to Their Surroundings?

SCIENCE CAPSULES

$ Anchoring Fibrils
$ Lupus Diagnosis and Survival

Science Capsules, continued

$ Genetic Studies of Systemic Lupus Erythematosus (SLE)
$ Friedreich=s Ataxia
$ The Brain=s Capacity to Change
$ A New Approach to Recovery After Spinal Cord Injury
$ Imaging Pain in Humans
$ Structural Basis of Multidrug Recognition Determined
$ Structure of Key Component in Programmed Cell Death Determined
$ Understanding Clathrin Mediated Endocytosis
$ New Explanation for Why Lactic Acid in Bloodstream Rises During Severe Injury, Sepsis, and Heart Failure
$ Crystal Structure of Enzyme That Produces Key Cell Molecule Determined
$ Molecular Basis of Spinal Muscular Atrophy Discovered
$ Broader Role of Telomerase in Extending Cell Life
$ Induction of Tolerance to Antigens
$ Genetic Determination of Type 1 Diabetes Autoimmunity
$ Intensive Therapy of Type 1 Diabetes Reduces Collagen-Based Complications
$ Prediction of Coronary Disease in Type 1 Diabetes
$ A Mathematical Model of Colonization by H. pylori, Pathogen in the Stomach
$ Cholesterol-rich Regions in Membranes are Key for Stress Effects on Blood Vessel Lining Cells
$ The Gene for Recessive Polycystic Kidney Disease is Mapped
$ Identification of a Membrane Protein That Protects Against the Inflammation of Glomerulonephritis
$ Diamond-Blackfan Anemia: The First Human Disease Caused by a Mutation in a Gene for a Ribosomal Protein
$ The Immunosuppressant Cyclosporine Causes Cancer Progression
$ A Cloned Zebrafish Gene is A Model for Human Congenital Anemia
$ A Red Blood Cell Membrane Protein is Important for Normal Membrane Integrity
$ Role of Niemann-Pick C1 Protein In Disease
$ Is a Low Leptin Concentration the Expression of the "Thrifty Genotype ?"
$ It Caught My Eye
$ Understanding Cataract Formation
$ Specificity in Visual Signaling Pathways
$ Organization of Neurons in the Cerebral Cortex
$ Analysis of Visual Motion
$ Rapid Visual Guidance of Movement
$ Mathematical Modeling of Rapid Eye Movements
$ Attentional Activity in the Cerebral Cortex
$ Pregnancy and Autoimmune Retinal Disease
$ Hereditary Factors Affecting Predisposition to Uveitis
$ New Insights into Hereditary Eye Tumors
$ Novel Roles of GDF-9 in Regulating Fertility

Science Capsules, continued

$ Understanding Early Miscarriage
$ Environment and IQ Level
$ The Role of Hormones in Maternal Behavior
$ Healing Damaged Spinal Cords
$ A Mouse Model of Host Defense Against Lung Inflammation
$ New Ways to Reduce Jet Lag on the Horizon
$ Genes That Control Early Brain Development
$ Powerful Anti-AIDS Agent Found in Tears and Urine of Pregnant Women
$ Maternal Caffeine Use and the Outcome of Pregnancy
$ A Better Way for Nurses to Assess Infant Pain
$ Clue to Excess Prevalence of High Blood Pressure in Blacks
$ A New Lesson From Sleeping Dogs
$ Inflammatory Findings on Diabetes
$ Homocysteine: Another Kind of Heart Risk
$ Too Much Ado About Mitral-Valve Prolapse
$ New Insights into Human Cell Aging
$ Declining Seroprevalence in New York City HIV Epidemic
$ Changing Drug Use Patterns
$ Who=s Using Methamphetamine? New Insights
$ The Environment of the Mouse Matters
$ Unraveling the Mysteries of Relapse
$ Further Evidence of the Association between Human Papillomavirus Infection and Cervical Cancer
$ Breast Cancer Genetics
$ Mechanisms of Angiogenesis
$ Functions of BRCA1
$ Identification of a Protein that Helps Maintain Genomic Stability
$ Prostate Cancer Genetics
$ Function of the Met Gene in Hereditary Papillary Renal Carcinoma
$ Hormone Levels, Dietary Soy, and Breast Cancer
$ What=s the Natural Purpose of a Marijuana Receptor?
$ The Way We Were: Making vs. Storing Long-term Memories
$ Genetic Locus for Specific Language and Reading Deficits
$ Competition Among Brain Chemicals Suggests New Path to Medication Development
$ To Sleep, Perchance, To Have a Memory Work-out
$ Generational Transmission of Psychopathology
$ Delaying Menopause-Related Health Problems: Estrogen Protection With or Without Fertility
$ Identified Protein May Lead to Gene Therapy for Huntington=s Disease
$ Neighborhood and Socioeconomic Characteristics Make It Difficult to Initiate and Maintain Recommended Physical Activity Levels
$ Centenarians Live Most of Their Lives in Good Health

Science Capsules, continued

$ Chronic Inflammation in the Elderly May Lead to Disability and Early Death
$ Researchers Identify Genetic Mechanisms Involved in the Age-Related Increase of a Blood Clotting Factor
$ Scientists Gain New Insights into Pathways Controlling Immune Function
$ Common Mechanism is Identified for Gene-Specific and X Chromosome Inactivation
$ One Form of the ApoE Gene Protects Brain Cells from Injury
$ Mutations in the APP Gene Inhibit Normal Protective Functions of the APP Protein
$ Can Tau Mutations Cause β-amyloid Deposition?
$ Gene Controlling Life-Span Identified
$ Lorenzo=s Oil Prevents Neurodegeneration in a Fly Model of Human Disease
$ New Gene Causing Dementia Discovered
$ Mammalian Clock Genes
$ Inhibition of Inappropriate Thoughts and Impulses
$ Cytomegalovirus Accelerates AIDS Progression in Infants
$ Human Myostatin Gene Expression Contributes to Muscle Wasting in HIV-Infected Men
$ The Eyes Have It
$ Effects of Low Level PCB Exposure on Male Reproduction
$ Chimp Origin of HIV Found
$ Weakened Virus Still Causes Disease in Primates
$ Routine Maternal Use of AZT is Safe for Children
$ Cellular Immunity May Not be Necessary for HIV/AIDS Vaccine
$ Possible Relief for Allergy Sufferers
$ Key Immune System Enzymes Essential to Health
$ Mast Cells Protect Against Bacterial Infection
$ Progress in Developing an RSV Vaccine
$ Powerful Skin Toxin Identified
$ Protein Signals May Be Linked to Leukemia
$ Isolation of a Potential Activator of Latent Herpes Simplex Virus
$ Sequence of Chromosome 1 of *Leishmania major*
$ Potential Candidate for Herpes Simplex Virus Vaccine
$ Disease Promoting Enzyme Targeted
$ Infection May be Risk Factor for Cardiovascular Diseases
$ Psychosocial Implications of XSCID
$ Isolation and Characterization of Human Cementoblasts
$ Mutations in GNAS1 Cause Fibrous Dysplasia of Bone
$ HistatinsCPromising Antifungal Agents
$ New Insights into Cartilage Development
$ Molecular Mechanism for Cleft Palate
$ Candidate Taste Genes Identified
$ Degradation of Oxidatively Damaged Histones Occurs Through Poly-ADP Ribose-activated 20S Proteosome

Science Capsules, continued
$ Cartilage to Bone: The Role of Vascular Endothelial Growth Factor (VEGF
$ Novel Ubiquitin Chains in DNA Repair
$ Apoptosis in the Absence of Caspase Activity
$ Report on the Health Effects of Electrical and Magnetic Fields
$ Cloning of a Novel Kidney Cytochrome P450 Enzyme that Metabolizes Fatty Acids

STORIES OF DISCOVERY
$ Helping Couples Conceive
$ Drug Exposed Children: What the Science Shows
$ Neurobiology of Addiction: The Role of Dopamine
$ The Link Between Oral Biofilm Infections and Systemic Disease
$ Friedreich=s Ataxia and Molecular Mechanisms of Iron Transport
$ Challenging Obesity
$ Sun and Skin
$ Fetal Alcohol Syndrome
$ An Appetite for Alcohol
$ Progress in Understanding Alzheimer=s Disease
$ Building HIV/AIDS Research Capacity in Uganda
$ A Simple Vision Plan

GPRA Working Group Assessment of NIH=s Performance: Goal A

The Working Group was charged with assessing NIH=s performance under Goal A. Their specific assignment was to review the research outcomes provided by the NIH and, by applying the assessment criteria (Table 5), determine whether NIH successfully met the goal, substantially exceeded the goal, or failed to meet the goal.

Table 5: Goal A Assessment Criteria

The NIH biomedical research enterprise ***has successfully met this goal*** when its research yields new findings related to biological functions and behavior, and the new findings are published and/or disseminated.

The NIH biomedical research enterprise ***has substantially exceeded this goal*** when, in addition to fulfilling the above criteria, any of the following apply:

$ discoveries result in significant new understanding of a particular biologic or behavioral process. Such new understanding may open up new avenues of research or be applicable to other disciplines, other areas of research, or other diseases.

$ research yields answers to long-standing, important biological and behavioral questions, or provides novel investigative approaches for addressing such questions.

$ genomic information about humans, model organisms, and/or disease-causing agents is translated into new understanding of the role of genes and/or the environment in human health, disease, and behavior.

$ discoveries have potential for translation into new or improved technologies, diagnostics, treatments, and preventive strategies.

Assessment Summary

In their discussion, described below, members of the Working Group identified a number of important themes or categories of research outcomes, discussed the significance of these types of findings, and highlighted a number of research outcomes that they judged to be especially noteworthy. The Working Group concluded that NIH had substantially exceeded the goal of adding to the body of knowledge about normal and abnormal biological functions and behavior. Specifically, the Working Group concluded that the outcomes demonstrated that NIH had sustained the excellence and responsiveness of the research systemCan important achievementCwhile demonstrating willingness to take research risks necessary to advancing biomedical knowledge, and ultimately human health.

Assessment Discussion: Research Outcomes and Their Significance

In an initial general discussion, the Working Group acknowledged the importance of maintaining a robust body of knowledge about biological function and behavior, because this knowledge underpins almost all translational and clinical research efforts. At the same time, the inherent nature of research makes it impossible to predict with any precision the timing or nature of the ultimate payoff of any given investment in basic science. Many of the dramatic changes that have occurred in American medicine over the past 50 years are based on insights drawn from the traditional biomedical sciences, such as microbiology, physiology, pathology, immunology, and chemistry. More recently, molecular biology, genetics, neuroscience, behavioral science, computer science, and imaging technologies increasingly have contributed to our understanding of the etiology and pathways of disease. All of these disciplines aim to elucidate not only the cause and mechanisms of disease, but also the characteristics of the healthy cell, tissue, organ, or organism.

Public announcements of exciting medical research breakthroughs can leave the public with the impression that discoveries are sudden and accomplished in isolation. In reality, medical breakthroughs are usually the culmination of many less-heralded discoveries achieved in the course of long-term and steady investments and efforts in basic and clinical research. Scientists rely on the work of others to enlighten their own pursuits; as such, knowledge is cumulative and breakthroughs often come when a critical mass of information has been gathered, most often following years of work by hundreds of investigators in a variety of disciplines. This is a phenomenon often under appreciated by a public anxious for instant cures.

The Working Group also highlighted a number of especially noteworthy outcomes that, in the judgment of the members, fulfilled the criteria for having substantially exceeded the goal. These advances fell into a number of broad categories: cell proliferation research, studies of gene function and expression, immunology, the biological bases of cardiovascular disease, the brain, learning, and memory, behavior studies, and population studies.

New Insights into Cell Proliferation and Cell Death. Research on the mechanisms of cell proliferation and cell death has the potential to uncover why it is that cells proliferate when they shouldn't, and also why they don't proliferate when they should. ›Cell proliferation‹ often has a negative connotation because of its association with the inappropriate, uncontrolled growth of cancer cells, but the flip side is its function in cell and tissue regeneration. The Working Group recognized an underlying unity in all of this biology, and that the outcomesCnew knowledge about normal and abnormal biological processesCare applicable to a broad spectrum of diseases and conditions, including cancers, autoimmune disorders, neurodegenerative diseases, birth defects, and trauma. The Working Group also emphasized that these important new insights are dependent upon a large body of knowledge amassed from many years of research in many different areas. For instance, many of the cell proliferation findings are important extensions of

major new understandings of the cell cycle, of biological damage control mechanisms, of genetics, and of the role of recessive oncogenes and susceptibility genes in human cancer.

The finding that, in a mouse model, a mutation in the breast cancer gene (BRCA1) leads to chromosome rearrangements in the region of a well-known tumor suppressor gene, p53, thereby leading to uncontrolled cell proliferation and the development of tumors, is a milestone for several reasons. Clearly, it adds significantly to our understanding of how cancer develops. The advance also underscores the importance of animal research, demonstrating that one can productively study human cancer genes in animals and recreate human disease in animals. This is the first such model that shows cancer development similar to the development of breast cancer in women. This animal model will be an important tool for future work on tumors and their progression. It can form the basis for screening and diagnostic tools, for testing drugs to prevent tumors in humans, as well as for testing the role of environmental agentsCsuch as radiation or environmental estrogenCin tumor growth. The advance also points to the importance of the fundamental, solid genetic research that preceded it, demonstrating that our understanding of cancer has progressed sufficiently so that, instead of searching for a needle in a haystack, scientists were able to design rational experiments that would reveal the role of the BRCA1 gene and its relationship to p53.

Another noteworthy outcome involved new understanding of how the tumor suppressor gene, PTEN, inhibits tumor cell invasion and survival. PTEN mutations are involved in prostate cancers, melanomas, brain tumors called glioblastomas, and breast, lung, head, neck and other cancers. The advance again stresses the convergence of basic research, human genetics, and disease. Because of our knowledge of basic cell signaling, we really can begin to understand what role this gene might play, particularly in metastasis and cell migration. For example, an important factor in eliminating cancer cells is determination of how a cell in the wrong location can be triggered to die, thus preventing uncontrolled growth, tumor formation, and metastasis. PTEN and the molecules it regulates provide one such mechanism; for instance, PTEN might be restored to tumor cells by gene therapy, thereby blocking tumor cell growth. In addition, detailed knowledge of how PTEN functions could also provide novel targets for developing drugs that mimic PTEN actions and suppress cancer progression.

The advance involving the creation of human cancer cells was also highlighted. After more than 15 years of attempts to create cancer cells in the laboratory, scientists succeeded by altering the expression of a defined set of genes and affecting at least four cellular pathways. This accomplishment again demonstrates the value of accumulated knowledge about the process and regulation of cell division, as well as the identity and function of oncogenes. The ability to introduce specific genetic alterations to transform normal cells paves the way for more precisely defining the biochemical pathways in the cell that must be disrupted in the development of cancer. This information will open new avenues for exploring the roles of various cellular pathways that become disrupted and for determining the sequence of events that must occur as

cancer develops. With this knowledge in hand, we can then develop rational strategies for attacking cancerCby developing treatments that target specific steps in cancer development. New treatment modalities arising from this have the potential to help an enormous number of patients.

Advances in stem cell biology, particularly neural stem cells, were deemed an especially noteworthy class of outcomes related to cell proliferation. During embryonic and fetal development, stem cells give rise to the complex array of cell types found throughout the body. Stem cellsCcells at an early stage of specializationCare also found in several adult organ systems, such as blood, intestine, and skin, where they are able to replace the more specialized or defined cells that are lost due to normal physiological turnover or injury. These stem cells are capable of continually reproducing themselves and serve to renew certain tissues throughout an individual=s life. For decades, however, scientists believed that the adult central nervous system could not repair itself, in part because it lacked neural stem cells. In the past several years, however, researchers have shown that stem cells are indeed present in the adult brain and spinal cord, and that they can be grown in culture and directed to act in similar ways as fetal stem cells.

The Goal A outcomes included a number of significant breakthroughs in understanding adult stem cells. For example, researchers found that stem cells continue to generate new nerve cells (neurogenesis) in some parts of the brain even in individuals aged mid-60s and beyond, demonstrating that neurogenesis continues throughout life. They also found that neurogenesis in the adult nervous system is a dynamic process that responds to both internal and environmental factors. Activities such as exercise, circulating hormones, learning, and an enriched environment can promote neurogenesis, while adverse conditions such as stress have a negative impact on the production of new nerve cells.

In addition, investigators obtained the first evidence, from studies in rodents, that adult neural stem cells can be used to repair damage from a broad array of brain disorders such as adrenoleukodystrophy, multiple sclerosis, Alzheimer=s disease, and many childhood brain disorders where cell dysfunction is Aglobal@ or spread throughout the brain. Investigators had previously believed that the promise of stem cells was limited to disorders such as Parkinson=s disease, in which damage is restricted to defined areas of the brain. Although promising, this result has only been seen in animal models. Obtaining stem cells from the brains of adults is very invasive.

In another fascinating set of studies, researchers answered an important unresolved questionCwhether stem cells in adult organs are limited to producing specialized cells of that organ, or whether they are capable of producing specialized cell types in other organs as well. The answer was that stem cells in the adult organism have a limited ability to become adult cells different from those of the donor organ. Specifically, it was demonstrated that bone marrow stem cells could give rise to liver cells and that neural stem cells became blood-forming cells.

These studies have only been done with non-human cells; it remains to be determined if human adult stem cells have this flexibility.

This new knowledge is significant for many reasons, not the least of which is that it changes the way we think about the brain and treatment for brain disease and injury. We used to think that once nerve cells died, there would be no replacement of them, so there is always and only a net loss of neurons. With these findings we now understand that the adult human brain has, in fact, a reservoir of cells which can proliferate. And not only can these cells be replaced, but the environment has some influence on this, and we are certainly in control of some of those environmental parameters. It is exciting to think about the fact that we can actually help ourselves if we understand what we should be doing to optimize replacement of neurons. These findings have obvious implications for the development of new treatment modalities for a number of devastating and different illnesses and injuries.

The ability to isolate and grow adult stem cells in the laboratory is very important as well. It paves the way for discerning the exact biochemical ›cues= needed to coax a cell of type A into becoming a cell of type B. It will also be possible to add genes, or take genes away, that is, to tailor the stem cells to the purpose for which they are needed. For example, if one wanted to replace myelin in a myelin-deficient disease, then having stem cells with the capacity to make the myelin-producing cells, and being able to grow those cells under optimal conditions could revolutionize the way we treat disease. The fact that neural stem cells are able to give rise to cells that are not neural, that is, they can become blood-forming cells is especially exciting. Blood stem cells have been particularly challenging to study because they are rare, difficult to isolate, and difficult to manipulate. The finding that neural stem cells, when put back into an animal can act like a blood stem cell, is quite amazing and unexpected. Neural stem cells are much easier to work with, and are much more susceptible to manipulations such as adding genes or directing them into certain pathways; however, as noted earlier obtaining neural stem cells from adults is very invasive. Basic studies with these cells will likely lead to advances in our knowledge of normal and abnormal cell growth, apoptosis (programmed cell death), and the behavior of the immune system, for example, in autoimmune diseases. It should be noted, however, that stem cells from adult tissues have not been shown to have the potential of pluripotent stem cells from fetal tissue or embryos, and may not prove as useful for the study of cell specialization as pluripotent stem cells.

Other outcomes were notable for increasing our understanding of diseases in which cells either prematurely die or undergo uncontrolled growth. Apoptosis (programmed cell death) is an important physiological process that ensures the elimination of damaged or unwanted cells in healthy individuals. Aberrant regulation of cell death (either too little or too much) contributes to the development of many disorders, including Alzheimer=s disease, AIDS, rheumatoid arthritis, and cancers. Previous research showed that chemotherapy to destroy tumor cells can be rendered ineffective by the family of anti-apoptotic proteins known as Bcl-2 and Bcl-X_L. An important

Goal A research outcome described new understanding of the molecular mechanisms of Bcl protein activity in human tumors and immune cells. Investigators demonstrated that Bcl-2 proteins can Aover express,@ making tumor cells resistant to anti-cancer agents. The effects of Bcl-2 can be, at least partially, overcome by bathing tumor cells with high doses of chemotherapy. Understanding the role of Bcl-2 in stopping or delaying apoptosis may lead to clinical applications. Illnesses related to early cell death, such as Alzheimer's disease, may be correctable by inducing expression of Bcl-2. Experiments are underway to evaluate whether mutant cells containing modified Bcl-2 proteins that cannot be Aturned off@ can protect blood-cell producing stem cells against high chemotherapy doses.

New Understanding of Cell Signaling. Cell signaling is another important biological process that we need to understand better. Cells in different organs of the human body process and integrate a huge amount of information about their local environment through a complex array of protein messengers. These messengers transduce signals from the outside of the cell across the cell membrane, through the cytoplasm and ultimately into the cell nucleus. In times of acute stressCeither environmental stress such as ultraviolet or ionizing radiation, or ›internal= stress in response to infection or cell injuryCcells undergo a precise and rapid response to the particular stressor. Movement or stimulation of specific proteins, called transcriptional activators, into the cell nucleus lead to alterations in gene expression in response to environmental stress. These changes in gene expression lead to the formation of new proteins that help the cell respond to the potentially harmful conditions. One such condition inside the body occurs during infection or cell injury in which specific cells induce cytokines, which trigger an inflammatory response. Chronic stress associated with inflammatory response can lead to wide number of diseases including heart disease, autoimmunity, asthma, arthritis, neuronal degradation, and cancer. In a series of seminal studies, NIH-supported researchers defined the precise molecular events that occur inside the cell to activate the expression of new genes in response to specific stress signals like those mentioned above. In order to better treat a broad range of diseases associated with pro-inflammatory signals (e.g., heart disease, asthma, autoimmune diseases), it is essential to understand the underlying molecular biology of the stress responses. These basic cutting-edge studies provide specific molecular targets for the development of novel intervention strategies in the treatment of these disease.

For some time, scientists have studied the roles of neurotransmitters (message-carrying chemicals) and their receptors in memory and learning. Powerful research tools have made it possible to delete or add neurotransmitter-related genes in laboratory mice and to determine the effects on living brains. For example, scientists added a gene to adult mice that altered the way a particular neurotransmitter receptor interacted with the neurotransmitter glutamate. In effect, they made the receptor more like the version of the receptor that is found in young mice. The mice learned faster, remembered more, and were able to apply what they learned. This is the first time that the alteration of a specific gene can be linked to improved learning in mice. And, since the receptor gene the scientists studied is very similar to the same gene in human brains, it now

appears that changing a gene to improve human learning abilities might someday be possible. While this insight is still an early development in the biological study of intelligence, it is encouraging news in the fight against age-related memory loss, senility, and Alzheimer=s disease.

Type 2 diabetes is a major disease for which genetic techniques are yielding potentially powerful new approaches to prevention and treatment. Type 2 diabetes affects more than 16 million Americans. It is characterized by a resistance to the action of insulinCthe hormone necessary for converting sugar, starches and other foods into energyCin many different tissues of the body. This is coupled with the inability of the pancreas Beta cell to deliver insulin in a regulated pattern and quantity to control the breakdown of the sugar glucose. The underlying mechanism causing insulin resistance is poorly understood. In order to gain insight into how type 2 diabetes develops and progresses, it is critical to understand the signaling pathways used by the cell protein that binds insulin (the insulin receptor) and how abnormalities in this system lead to insulin resistance. One especially laudable outcome in this area involved the application of a technique that uses specially developed genes that act as >molecular scissors= that can recognize, target and cut out segments of genetic material. In this case, the method was used to delete the insulin receptor in the pancreatic beta cell to address the question of whether disruption of insulin signaling in the beta cell could contribute to an alteration in its function. Mice showed a selective loss of insulin secretion in response to glucose and progressively impaired glucose tolerance. These findings provide direct evidence of a functional role for the insulin receptor in the maintenance and balance of glucose levels and suggest that defects in insulin signaling in the beta cell may contribute to the observed alterations in insulin secretion in type 2 diabetes. An understanding these events has implications for new approaches to both treat and prevent this disease.

New Insights into the Function and Regulation of Genes. Many of the outcomes deemed outstanding by the Working Group added to our understanding of the complexities of gene expression and the basic cellular functions that underlie human development. For example, a number of research outcomes characterized how small signaling molecules control normal cellular function and how changes in the genetic coding for these signals can result in abnormal levels of normal human biological agents.

A number of important outcomes provided new insights into obesity and alcohol consumption and the complex pathways in the brain that control appetite and food intake. For example, researchers learned that alcohol consumption and resistance in animals are inversely related to levels of neuropeptide Y, a potent appetite-stimulating hormone in the brain. This finding adds to our understanding of physiological mechanisms that underlie alcohol use and provide important clues about drinking-related phenomena in humans. Scientists will continue to decipher how these mechanisms interact to form circuits in the nervous system that regulate behaviors, such heavy drinking, that are harmful to health, and have potential for interventions. Investigators also identified a gene (called mahogany) in mice that is involved in energy balance

and weight regulation. They also identified a human equivalent of the mahogany gene and were surprised to find that the human gene also plays a role in the immune response. This observation provides new insight into the regulation of energy metabolism and indicates a relationship between an essential part of body weight maintenance and immune function. Another finding was that deletion of the mouse gene for the appetite-stimulating hormone known as melanin-concentrating hormone resulted in an increased metabolic rate and leanness and reduced body weight. This new information on pathways that control food intake has led to fundamental advances in our understanding of body weight regulation. In addition, we now know that systems that control energy expenditure are also important in this process. These findings have important implications for the development of therapeutic agents that target these complex pathways to control appetite and treat obesity. In another advance, researchers identified an enzyme that, when blocked, partially restored insulin sensitivity in diabetic mice and also allowed the mice to consume a high fat diet without gaining weight. This suggests that drugs that block the enzyme could be useful in treating diabetes and obesity. Obesity is of concern because it is a risk factor for the nation's number one killerCheart diseaseCas well as for diabetes and other chronic conditions. Novel approaches to appetite regulation have obvious implications for obesity, but also for other serious health problems such as diabetes and alcoholism. In addition to improving overall health, outcomes such as these have important implications for controlling health care costs.

The genetic contribution to inflammatory diseases also is being unraveled. NIH scientists and international collaborators have discovered genetic mutations on chromosome 12 underlying a newly recognized group of inherited inflammatory disorders that includes familial Hibernian Fever. This discovery may lead to treatments targeted at the cellular level, which could displace the current treatment of steroid administration, which can have serious side effects.

The Working Group lauded an unlikely partner in understanding human genes, human development, and human diseaseCthe zebrafish. Zebrafish have many genes in common with humans, and the ease of working with zebrafish has facilitated the identification of a number of important human disease genes, including those involved in anemia and porphyria, an inherited disease characterized by a disabling sensitivity to sunlight. Zebrafish are by no means the only critical research tool for deciphering the function of genes. With the imminent completion of the DNA sequence of the human genome, the challenge will be to identify thousands of genes and determine their role in health and disease. To facilitate these studies, scientists need a critical research tool, a catalog of the full repertoire of human genes. In early FY 1999, the NIH launched a major effort to develop such a tool. Researchers are already producing cDNA clone collections that contain full-length copies of many human genes, sequencing these cDNAs, developing the associated informatics tools, and creating a publicly accessible website to provide up-to-date information to the research community. The generation and availability of clones and sequences of the complete set of human genes and those of other mammals will be an essential

research tool that will enable researchers to readily explore the function of genes and further our understanding of biology and human health.

Gene therapy advances in animal models also were highlighted as evidence that NIH has exceeded Goal A in the past year. One outcome addressed a significant phenomenon of the aging processCthe fact that mammals, including humans, lose up to one-third of their skeletal muscle mass and strength. In humans, this loss occurs gradually between the ages of 30 and 80. Researchers found that if they caused increased production of a protein involved in the growth and maintenance of skeletal muscle (insulin-like growth factor 1 or IGF-1) in the muscles of old mice, they could stimulate growth and increase strength of existing muscle fibers. This outcome suggests that muscle-specific delivery of IGF-1 could form the basis of a human gene therapy for preventing or reversing the loss of muscle mass and strength associated with aging and functional impairments due to muscle diseases.

Basic Advances in Immunology and Infectious Disease. The Working group noted that immunology is a rapidly advancing field; in the last two or three years there has been a virtual explosion of basic science and applied findings. It is definitely a field of biology that is well poised for the translation of basic findings into clinical research and then to clinical medicine. Advances in immunology are having an extraordinary impact on medicine, ranging from bone marrow transplantation, to new treatments for HIV infection, to enhancing the immune system against tumors, to new drugs for preventing the rejection of transplanted organs. A number of research outcomes within Goal A were hailed as examples of remarkable new understanding of basic immunology that have the potential for leading to new treatment and prevention modalities.

One outcome concerned the discovery of a family of proteins (toll-like receptors) that are involved in the body=s immune response to bacteria. When these proteins detect and signal the presence of the bacteria, they trigger a severe immune reaction that can lead to septic shock. This new knowledge could facilitate development of new vaccine strategies and new approaches to the treatment of septic shock. Drugs that could interfere with the activation of toll-like receptors by bacteria during an acute infection could save thousands of lives by blocking the septic shock signaling cascade. Toll-like receptors may also provide new avenues for the rational design of vaccine adjuvants, which are mixtures of biologically active materials that boost immune responses to antigens. The design of new adjuvants that elicit stronger, longer lasting immune responses, with reduced toxicity, would be a major advance in vaccine science.

A number of other seminal advances documented new understanding of the effect of HIV infection on the immune system. The Working Group noted in particular that research findings on HIV will likely have a significant impact on world health. The new combination antiretroviral therapies for HIV infection are allowing many patients to live longer, healthier lives. The therapies can suppress the replication of HIV-1 to the extent that the virus is undetectable in the blood, raising hopes that HIV infection could be eradicated and infected patients could be

Acured@ after several years of combination therapy. Researchers found, however, certain immune cells (CD4+ T lymphocytes) can harbor a latent form of HIV-1 even in treated patients who have had an undetectable viral load for 20 months or more. The infected immune cells form a long-term, latent reservoir of HIV that will replicate if these cells are activated. Scientists estimate that HIV virus can persist in these immune cells for more than 60 years. This new knowledge has given physicians and investigators a new perspective on how long we may need to treat patients, and the importance of finding other ways to truly eliminate the last vestiges of HIV in patients undergoing antiretroviral therapy. Scientists will need to develop more effective and less toxic long-term medications to suppress HIV replication. Strategies are needed to accelerate the death of latently infected cells, to boost the immune system=s response to HIV released from reservoirs of these cells, and to purge all residual virus from the body.

Another outcome related to lymphocytes and HIV infection has to do with the function of the thymus gland. The thymus gland is a major site for the production and generation of T cells, which play a critical role in the immune system=s defenses. Thymic function is very active in infants and young children, and then believed to decline sharply, thus affecting the ability of the thymus to reconstitute T cells that are lost during HIV infection. Researchers developed an assay to identify T cells that recently left the thymus and thus could serve as a marker (indicator) of thymic output and function. They found that although thymic production of new T cells declines with age, it remains substantial into late adulthood (even mid 70s) rather than being limited to infancy and early childhood, as had been previously believed. Scientists also found that although adult patients infected with HIV had suppressed thymic function, most showed a progressive and sustained increase in new T cells following infection suppression with antiretroviral therapy. This knowledge offers significant hope that an HIV-ravaged immune system may be able to rebuild itself after intensive antiretroviral therapy. Therapies that directly improve thymic function may also increase the rate of immune reconstitution after antiretroviral therapy. In addition, methods for tracking newly produced T cells are valuable tools for monitoring immune reconstitution in HIV-infected people.

Other AIDS-related outcomes focused on how AZT and many other anti-AIDS drugs target an enzyme in the HIV known as reverse transcriptase. This enzyme translates the virus= genetic material into a form that can insert itself into human chromosomes. The virus then commandeers the infected cell, forcing it to produce new virus particles. Scientists have been trying for years to determine the structure of reverse transcriptase in its active form. In a recent advance, researchers succeeded by using an innovative chemical technique to tether the enzyme to its natural biochemical partners and develop a detailed, three-dimensional snapshot. The new information reveals in atomic detail how the enzyme foils AZT and how HIV becomes resistant to AZT-like drugs, and suggests a possible target for new anti-AIDS therapiesCa small pocket that, if plugged by a drug, might shut down reverse transcriptase, and thus halt viral replication. These findings have applicability to other viruses that develop drug resistance.

Finally, basic immunology studies have led to new understanding of why a woman=s immune system does not recognize the developing fetus as a ›foreign= body that should be rejected. Recent findings shed light on how the immune system controls critical interactions between immune cells known as natural killer cells and embryo cells during early pregnancy. These interactions probably ensure the formation of a successful implantation site for the developing embryo. Thus, the advance could illuminate early pregnancy loss. In addition to elucidating a very specific function, fetal immune privilege, as a clue to the mechanisms for achieving tolerance to specific antigens, this knowledge provides insights on global aspects of immune regulation.

Another outcome provided new information about a major concern of parents of young children. Otitis media (middle ear infection) is one of the most significant health problems for children in the United States, costing approximately 4-5 billion dollars annually and accounting for the most common reason for a sick child to be treated by a physician. Investigators discovered the steps by which bacterial and viral infections cause otitis mediaCrespiratory syncytial virus (RSV) is the principal virus invading the middle ear, and it enhances attachment of a common bacterium known as *Haemophilus influenzae*, a crucial step for bacterial induction of otitis media. This knowledge is critical for the development of targeted clinical interventions such as vaccines and other strategies designed to block the infectious process. RSV is known to be the most significant causative agent of pediatric respiratory tract disease worldwide. To date, RSV vaccine development has been hampered by the inability to grow RSV in the laboratory for study purposes. An important outcome highlighted the fact that scientists recently engineered a strain of RSV that can be maintained in tissue culture, an achievement will facilitate further laboratory studies on RSV and may facilitate development of an RSV vaccine.

Basic Science Relevant to Heart Disease. It is unusual, but accurate, to think of humans as electrical beings. Like any good machine, humans are controlled by electricity. Our bodies are made up of a vast network of interactive electrical components more intricate than those of any supercomputer. The Working Group highlighted a stunning advance that has furthered our understanding of the electrical properties of the human body by providing important insight into how potassium ions flow from cell to cell, through protein channels that open and close in response to biochemical stimuli. Scientists were able to solve the structure and determine the electrochemical properties of a specialized potassium channel that helps regulate heart rhythm. Defective versions of this channel underlie one form of a serious genetic heart condition that causes irregular heartbeat and sudden death (long QT syndrome). Potassium channels are critical for many bodily functions, including heartbeat, nerve signaling, digestion, and insulin release. A better understanding of potassium channels may help scientists develop drugs to treat diseases ranging from heart ailments to diabetes to epilepsy.

Scientists have long known that folic acid, one of the B vitamins, can protect against certain birth defects that develop shortly after conception. An important outcome described a more recent

findingCthat folic acid speeds up the conversion of homocysteine (a potentially harmful compound) to the amino acid methionine. Homocysteine has been implicated in heart attacks, strokes, and atherosclerosis. Scientists are now studying the mechanisms by which this conversion occurs, which could lead to approaches for preventing or treating heart diseases.

In atherosclerosis, another common cardiovascular disease affecting millions of Americans, deposits of plaque obstruct coronary arteries and other blood vessels. Thus, much research has been conducted on developing ways to promote angiogenesis, or the growth of new blood vessels in order to circumvent coronary arteries obstructed by the plaque deposits. The Working Group commended an outcome that provided a very different perspective on this problem. Researchers determined that angiogenesis may actually *contribute* to the progression of atherosclerosis. These findings strongly suggest that the formation of new blood vessels is an important prerequisite for atherosclerotic plaque growth. With this knowledge, scientists may be able to develop new treatments to slow the development of atherosclerosis, thereby delaying the progression of heart and vascular diseases, and perhaps reducing the incidence of heart attacks and strokes.

Understanding the Neuronal Bases of Learning, and Memory. For many years it was thought that we are born with a set number of brain cells. The recent and notable finding that new neurons actually do develop throughout life has changed the way we think about learning, other brain processes, and age-related cognitive disorders. One theory is that new neurons do not form in the absence of learning. Investigators found that neurons are indeed generated in response to the challenge of new learning and they survive longer when learning is taking place. Thus, learning, practicing, and remembering are all activities that seem to be linked the development of neurons. This insight has implications for therapies for individuals with learning disabilities and brain damage. In another remarkable outcome, researchers showed how subtle alterations in the cellular and molecular mechanisms underlying synaptic change during development and in adulthood might contribute to devastating brain disorders such as schizophrenia.

In another exemplary advance, researchers showed that the activity of brain cells (neurons) play a profound role in shaping cellular extensions (dendrites) during brain development and that neuronal activation within the living brain can initiate rapid changes in the structure of neurons. Signals between neurons are communicated at many sites along the dendrites and, since neurons that perform similar functions in the brain have similar shapes (much as the branching patterns of trees of the same species are similar), scientists have suspected that a neuron=s branching pattern must be important to the cell=s normal functional role. Neuronal shape changes are likely to play important roles, not only in the generation of new connections between neurons, but also in more subtle rearrangements of existing connections. The findings of this research have fundamental implications for how, at the cellular level, on-going neuronal activity plays a major role in the shaping of the brain=s architecture, and hence, its function. Over time, these kinds of changes in cell shape, in response to the actions of specific neurotransmitters, may explain how the young,

developing brain shapes its structure. These structural changes may also be involved in important changes in brain cell function that occur during development, such as learning. In addition, if such induced changes are found to occur in adult as well as developing animals, the changes may be involved in adult memory storage, as well.

The finding that babies react with far less interest to the speech of depressed mothers than they do to non-depressed mothers because the pitch and tones in a depressed mother=s voice do not promote attention or learning in a baby was also considered important. Since babies who experience early difficulties in learning often have problems later in behavior and school performance, we can now focus on strategies to prevent learning and behavioral problems.

Outcomes that focused on early insults to the developing brain and their consequences were also noteworthy, such as the advance which documented long lasting changes in the electrical activity of brain cells as a result of fever-related seizures. The changes occurred in the hippocampus, a region of the brain critical in epilepsy. This is important information, because there has been considerable controversy about whether febrile seizures cause epilepsy later in life; many adults undergoing surgery for intractable temporal lobe epilepsy report a history of prolonged febrile convulsions. If febrile seizures are indeed benign, children do not have to be put on medication. If, on the other hand, febrile seizures have long-term adverse effects on the brain, medications to prevent seizures or their consequences may be warranted. This new avenue of investigation should provide critical insights into how seizures affect the brain that may be relevant to many forms of epilepsy.

The discovery that the Pin1 enzyme may function in untangling the knots of protein that are a hallmark of Alzheimer=s disease was also deemed noteworthy. Interestingly, tissue inside the brains of people with Alzheimer's disease is conspicuously short of available Pin1, because Pin1 is apparently depleted by working overtime to keep fixing tau. This suggests that this critical enzyme somehow is unavailable to repair tangles as they form. Pin1's detangling job is not limited to the brains of people with Alzheimer's disease. The enzyme also juggles phosphate-tagged proteins that regulate the timing of cell division in many different cell types. This new knowledge may aid in the quest for new therapies to treat Alzheimer's disease and other disabling neurodegenerative diseases.

The Brain and Behavior. Behavioral studies are important to determining the complex interplay between genes, behavior, and the environment. Important outcomes from NIH-supported studies are delineating the role of diet, lifestyle, and occupation on health and the onset of disease. For example, cigar smoking is on the rise, based on the perception that it is safer than cigarettes. However, investigators recently determined that cigar smokers are at increased risk for cancers of the lung and throat/upper airway, cardiovascular disease, and chronic pulmonary disease. We now know that, far from being a >safe= form of recreation, cigars pose significant health risks, and

their increasing popularity is rapidly emerging as a serious public health problem requiring behavioral and educational interventions.

Finding ways to change dietary patterns to improve health has long been a goal of behavioral research. A notable outcome suggested that fish oil (which contains omega-3 polyunsaturated fatty acids) directly affects cardiac electrical activity and reduces the incidence of life-threatening arrhythmias that result in sudden cardiac death (SCD). The overall incidence of SCDCwhich claims the lives of more than 250,000 individuals in this country each yearCmight be markedly reduced by a diet that includes fatty fish. Since there are currently no effective therapies to prevent SCD in individuals with no history of heart disease, any reduction in the incidence of SCD would be a tremendous step forward.

Other significant outcomes spotlighted the complex relationships between behavior and genetics. The finding that high levels of the appetite stimulant neuropeptide Y increase food intake but low levels increase alcohol intake could lead to important clues about drinking-related problems in humans. Other addictive disorders with strong behavioral components are being studied to understand the underlying neurobiological processes. For example, one important advance indicates that dopamine=s role in addiction is more complex than was previously thought. New findings in animals suggest that although dopamine may act to make new experiences more pleasurable, once the pleasurable task is learned dopamine=s role is diminished. While the dopamine system is still important, it appears that its role may be particularly critical in the initial response to drugs of abuse and that other neural systems may become more critical as an individual progresses from initial drug use to addiction. Thus, drug treatment approaches need to be designed that focus on more than just blocking dopamine. Identification of the role that other brain systems play in addiction will be important in our efforts to treat addiction and relapse.

Population Studies Provide Fundamental Knowledge About Biology, Behavior, and the Environment. Clearly, understanding human behavior and how it is modulated by genetics and environmental factors increasingly will be a central component of preventing and treating many of the chronic diseases facing us today, such as cancer and heart disease. Outcomes from population-based studies have yielded important information about gender, racial, and ethnic differences in disease morbidity and mortality, as well as the relative of role of environment and socioeconomic status in health and disease. The results of these studies provide intriguing insights into, and raise challenging new questions about the relative roles of behavior, biology, and the environment in human health. For example, an especially noteworthy finding focused on the impact of health on economic resources. Another outcome addressed the biological and behavior aspects of substance abuse and addiction, providing information that will be useful for determining how various interventions affect not only health outcomes but also costs. The finding that overall heart disease morbidity and mortality rates in diabetics are not dropping as rapidly as they are in non-diabetics highlights the importance of learning why diabetes is not particularly responsive to current interventions to prevent or treat heart disease. Important

gender differences in heart disease have also been highlighted through population studies. Animal studies revealed gender differences in heart muscle contraction, which may be due to calcium metabolism and response to beta adrenergic stimulation. These differences suggest that different medications or doses might be needed for women as compared to men.

This page left intentionally blank

CHAPTER 3

Goal B: Develop New or Improved Instruments and Technologies for Use in Research and Medicine

Introduction

Recent advances in medical research and health care are closely linked to the development of new instruments and technologies. Improvements in the early detection of cancers, technologies to better visualize the living body in both normal health and disease states, and new ways to identify and target abnormal cells and tissues will provide a wealth of knowledge that can lead to new and improved diagnostics, treatments, and prevention strategies.

Many of the advances in medical science today, including the mapping of the human genome and brain imaging, have been the result of the development of advanced technologies and instruments that permit investigators to explore the human body in ways previously undreamed. The continued development of new technologies and instruments is vital to sustain the pace of medical discovery.

Instrumentation also includes computers, computer programs, and databases. The information generated by researchers, the information needed to conduct clinical trials, and the information required for the optimal practice of medicine have long ago exceeded the capacity of pre-computer methods. Now it is essential that we continue to improve methods for storing, analyzing, disseminating, and using new information in all the areas of biology and medicine. It is critical that we have the capacity to integrate the vast array of emerging genetic information into formats that are accessible to scientists worldwide, to establish new databases for visualizing 3-dimensional protein structures, to catalog the Amolecular fingerprints@ of genes that are turned on during the development of particular cancers, and to disseminate in a timely fashion critical information regarding public health and medical research.

Bioengineering encompasses a number of exciting technologies with enormous potential for improving the quality of life. One of the strengths of bioengineering as a discipline is that it integrates principles from diverse arenas, crossing the boundaries of biology, chemistry, mathematics, engineering, and physics, as well as medicine, academia, and industry. Research in biomaterials science, for example, expands our knowledge of how synthetic materials interact with body tissues, leading to development of new and enhanced implantable devices, improved

therapeutic procedures, and more accurate delivery of drugs to particular body sites. Research on acoustic, electric, and magnetic field effects and how they can be used to produce images has led to developments in bioimaging that have revolutionized diagnostic procedures. Research on imaging and signal processing have resulted in devices that have made it possible to scale up human DNA sequencing, which in turn is transforming the way biotechnology and pharmaceutical companies approach therapeutic drug development. And progress in chip manufacturing and micro fabrication are providing tools for biologic discovery that will forever change research on the cause and treatment of most diseases.

Overview of the NIH Research Outcomes Provided for Goal B

The NIH Institutes and Centers provided 69 science advances, science capsules, and stories of discovery that, in their judgment, demonstrated the development, or a critical step in the development of, new or improved instruments and technologies for use in research and medicine (see Table 6).

Many of the research outcomes that address Goal B are imaging technologies. Some of the most exciting advances in the area of imaging involve radiological imaging. For example, in the past five years, a new type of imaging modalityChelical computed tomography (CT) scanningChas been used to acquire detailed images of a large body region during a single breath hold. These images are then converted into elaborate three-dimensional models of the interior of anatomic structures in a way that simulates conventional endoscopy. One outcome documented how researchers developed a method to use these simulated endoscopies to automatically locate tumors in the air passages of the lungs. Another outcome described that spiral CT imaging has been demonstrated to be an effective, noninvasive screening tool for detecting lung cancer at an earlier and more treatable stage. A new form of magnetic resonance imaging (MRI) has also been used to detect subtle degenerative changes in cartilage that occur with the onset and progression of osteoarthritis. This application could eventually enhance a physician=s ability to to diagnose osteoarthritis, intervene with appropriate therapeutics, monitor clinical outcomes, and evaluate potential new therapies, including cartilage-protecting drugs and gene therapies.

Other advances in this area included new applications of current imaging technology. For example, researchers used MRI to determine that brain volume is more reduced in alcoholics than in non-alcoholics, and that the reduction is more pronounced in alcoholic women than it is in alcoholic men. Contrary to what was believed and/or previously reported, however, volume of the hippocampus (an area of the brain involved in memory, emotion, and cognition) was not selectively affected by alcoholism, nor by post-traumatic stress disorder. In another outcome, investigators employed adaptive opticsCoriginally developed for astronomyCto image the three types of photoreceptor cone cells in the intact living retina, obtaining the clearest views yet of the retina. In yet another imaging advance, scientists used a relatively new technique known as two-

photon microscopy to image living animal embryos over an unprecedented period of timeChours and even daysCwithout sustaining light-induced cellular damage.

Other outcomes focused on new analytical methods that, when combined with current imaging technology, provided important new insights into the brain. For example, one outcome involved the use of new mathematical and analytical methods for using functional magnetic resonance imaging to measure specific brain activities that unfold over time. This new methodology overcame a significant technical barrier and offers significantly improved temporal resolution and paves the way for further advances in event-related neuroscience. Other investigators developed an integrated suite of software programs for use with MRI to decipher the organization and function of different areas of the cortexCthe topmost layer of the brain responsible for many higher mental functions. Previous efforts to visualize this area of the brain were stymied by the intricately folded topography of the cortex. The new methods already have been used to generate the first surface-based atlas of human cerebral cortex and promise to be invaluable for studying the normal functioning of human cortex as well as the many different neurological diseases and psychiatric disorders that involve abnormalities in cortical structure and/or function.

Safe and effective imaging compounds are an important component of imaging technologies. One advance highlighted the development of a new and safe neuroimaging compound for studying human brain receptors for nicotine. This should lead to a greater understanding of how these receptors mediate nicotine=s many effects, which will in turn lead to new ways to promote smoking cessation and to treat cognitive deficits associated with neurodegenerative diseases such as Alzheimer=s disease. Another outcome described new methods for >labeling= the living brain=s respiratory pacemaker cells with dye so that they can be identified and researchers can then use microscopy and sophisticated electronics and study their electrical behavior.

By no means did all of the Goal B outcomes involve imaging technologies. A number of the discoveries involved technologies for gaining new molecular insights into biological systems. For example, NIH scientists recently devised a Web-based subtyping system that simplifies monitoring of the genetic variability of subtypes of HIV-1. This will make it possible to track the metamorphosis of HIV-1 as it spreads and to detect novel and potentially dangerous new strains more easily, and will also inform vaccine development efforts.

Other advances were in the field of structural biology. The relationship between a molecule's structure and its function is at the root of both normal and abnormal biochemical processes. Since molecules that share similar underlying amino acid or DNA sequences often share similar structures as well, an important area of research focuses on methods of accurately predicting a molecule's structure based on its underlying sequence. For example, investigators have designed a powerful software package for viewing and comparing the three-dimensional structure of molecules, providing an integrated approach to combined analysis of sequence and structural similarities. This new analytical capability arms researchers with a versatile tool for taking a

molecular sequence for which structural and functional information is lacking, mapping that to a model structure, and thereby gaining insight into its potential function in living cells. In addition, NIH researchers won a competition with a new technique for predicting protein structure.

Important improvements in determining protein structures have been accomplished with synchrotron radiation, which produces intense, brilliant X-rays that, when directed at crystallized molecules, are deflected in a way that allows scientists to deduce their structure. For example, new, third-generation synchrotrons allowed scientists to produce the world's first 3-D x-ray movie of a molecular reaction on a timescale of nanoseconds, or billionths of a second. The movie revealed how the molecule myoglobin changes its shape as it performs its primary functionCcapturing and releasing oxygen in muscle cells. The molecular movie of myoglobin reveals otherwise hidden structures that may aid in the development of new therapies and could shed light on how other oxygen-binding molecule work as well, such as hemoglobin in red blood cells.

Technical advances in assisted reproductive technologies tested in animal models were reported that will enable scientists to study the use of these technologies for infertility treatment and may allow endangered species to be preserved. For example, for the first time, researchers have successfully refined intracytoplasmic sperm injection (ICSI) procedures to the point that they were successful in producing the first rhesus monkeys using this method. Other investigators researchers successfully overcame difficulties in creating transgenic animals in other mammalian species by modifying and improving ICSI methods that introduce foreign genes into eggs.

Several other technological advances improved researchers= ability to study the immune system. For example, scientists have developed a technique to genetically >mark= mouse memory T cellsCcells that allow the immune system to attack invaders it has previously encounteredCan achievement potentially useful for vaccine development and for studies of natural immunity, transplantation, immunodeficiencies, and autoimmune diseases. Other researchers developed a safe technique for directly monitoring the body=s production of immune cells. Using this technique, they demonstrated that HIV infection shortens the life span of specific types of T-cells without a compensatory increase in T cell production rates. These observations contradict the popularly held belief that HIV kills infected T cells and induces a transient increase in T cell production, which eventually exhausts the immune system and causes death. The new findings also suggest that stimulating T cell growth may represent another means by which AIDS can be treated. Other investigators recently developed a novel method to identify specific T cells activated during an immune response. Using this methodology, scientists identified hepatitis C-specific T cells which play an important role in the development of liver injury as well as clearance of the virus, and found these cells in the blood and liver of hepatitis C-infected patients. Direct measurement and characterization of these cells using this novel method should extend our understanding of the immune reactions in the development of the disease and the mechanism of clearance and persistence of hepatitis C virus.

A number of discoveries highlighted for Goal B involved the development and improvement of devices that allow individuals to live healthier, more productive lives. Bioengineering advances have been particularly helpful to individuals with communication disorders. This includes an implantable device for the treatment of vocal fold paralysis; and a cost-effective, user-friendly listening system that allows individuals with hearing impairment to receive pilot and flight attendant announcements and other audio inputs available on aircraft, and to communicate with neighboring passengers. A clinical trial comparing commonly used hearing aid circuits demonstrated clearly that hearing aids provide significant benefit to patients, particularly in the form of improved speech recognition, both in quiet and in noise conditions. Another outcome documented that cochlear implantsCneuroprosthetic devices that convert sound into electrical currents that stimulate the nerve that transmits sound to the brainChelp hearing-impaired children in speaking and in recognizing speech. A surgically implantable neuroprosthetic device known as the Freehand System is enabling some individuals who are quadriplegic to grasp, hold, and release objects. In other neuroprosthetics research, recent experiments in rats gave some inkling of what the future may holdCby wiring directly into the brain, scientists have enabled rats to control a robot arm just by thinking about it!

In addition to advances in mechanical and electrical devices, scientists can assist patients with artificially grown tissues. Scientists developed a novel ›bioreactor= system that mimics the fetal cardiovascular environment, and then took cells from adult pig arteries and grew them in a biodegradable framework under pulsatile conditions imitating that of a heart beat. When the vessels were implanted into pigs where they appeared to function like normal arteries for up to 24 days. Another advance described how artificial skin has been developed using non-cellular components such as sugars and cow collagen.

Goal B outcomes also included advances in gene therapy, which uses genetic material to treat disorders, by either supplying the corrected gene, by turning off or on inappropriately activated genes, or by correcting the genetic defect. One hurdle in this type of therapy is delivering the gene to the correct cells and tissues. An important advance in the past year was the development of a new strategy that appears promising for both drug delivery and gene therapy. Investigators devised a method that uses an antibody to deliver either proteins or genes to endothelial cells in the lung. In animal studies, the method was successful in delivering a protein that protected lungs from oxidative injury. Another advance in gene therapy involved a successful strategy for increasing the abundance of gene-modified blood-forming stem cells in experimental animals. Initial safety studies of a form of gene therapy for mitigating impaired circulation in the heart demonstrated growth of new blood vessels and evidence of clinical improvement in the recipients. This is a very promising step toward developing less invasive approaches to treating coronary heart disease.

Many Goal B outcomes described new and improved tools for analyzing entire genomes and characterizing genes essential in healthy and disease states. For example, progress in sequencing

the human genome described one outcomeCthe sequence of one billion of the approximately three billion bases in the human genome was completed. This important milestone marks the success of the transition from the pilot to the full-scale production sequencing, and an international consortium of researchers is on track for imminent completion of the working draft of the human genome and the final, high quality genome sequence by 2003 or earlier. Another advanceCnoting that technologies used to perform the sequencing have become faster, more accurate, and less expensiveCdescribed how high throughput sequencing using automated capillary array electrophoresis has been developed into commercial instruments for widespread use. These instruments sequence DNA much more rapidly with much less human intervention than has been required for sequencing with the previous generation of semi-automated slab gel instruments. In fact, the majority of the human genome sequence is now being determined using these machines. In addition, an updated map of the human genome has been developed. The map identifies the chromosomal locations of about half of all human genes, featuring over 30,000 genes. A new technology known as radiation hybrid mapping was used to develop the map, which will provide a ›scaffold= on which to mount the large-scale sequencing data being generated daily as the sequencing of the human genome progresses. The map will also accelerate the pace of the discovery of human disease genes by positional cloning. One outcome described a complementary and timely information resourceCa Web-based service that provides a comprehensive view of the integrated mapping and sequencing data for the human genome. This information resource provides a framework for the integration of many types of chromosomal information and has great potential to accelerate the process of disease gene identification and analysis.

Another outcome described the development of ›DNA chips= or microarrays consisting of DNA from nearly all of the yeast genes. These microarrays allow for highly rapid, efficient and comprehensive studies since scientists can ask questions about all the genes in one experiment rather than one gene at a time. The yeast microarrays have been used to monitor gene expression and gain insight into complex biological processes, such as metabolism, gene regulation, sexual reproduction, and evolution.

Several Goal B outcomes featured single nucleotide polymorphisms, or SNPs. A SNP is a place in the genetic code where DNA differs from one person to the next by a single base, resulting in slight genetic variations between human beings that may predispose some people to disease. SNPs are useful genetic markers that allow researchers to find associations between genes and a disease. One advance highlighted computer simulations that have helped researchers determine that about half a million SNPs would be required for whole-genome association studies to locate susceptibility genes for common diseases that have multiple genetic components. Another featured the DNA Polymorphism Discovery Resource, which contains 450 DNA samples from unrelated, anonymous individuals of diverse ethnic backgrounds and is being used for SNP discovery. In addition, a database of SNPs has been established as a central, public repository for

this data, which, together with other SNPs resources, has the potential to speed the identification of genes associated with diseases.

Other genetic tools that were highlighted include: a novel assay for the analysis of ›chromosome healing,‹ a process which is important for the ability of stem cells to divide infinitely; a sensitive new technique for rapidly analyzing and characterizing bacterial DNA fragments; a computer program to detect subtle but significant relationships between protein sequences; and a new technique for measuring the activity of genes in cells.

Some research outcomes involved the development of new materials created for biological uses. For example, researchers discovered a method for creating a new class of porous materials with an orderly arrangement of ultra-small spherical spaces. One potential use for these materials is in the development of more stable and longer-lasting glucose sensor for the treatment of diabetes. A promising new technology for tissue engineering uses a polymer matrix system to achieve sustained release of DNA for up to a month. This system might one day be used to repair or replace body tissues and organs, or in gene therapies. For the first time, researchers have designed and synthesized a molecular-scale motor that transforms chemical energy into controlled, unidirectional rotary movement. This research provides a basis for the design of biological devices and instruments that are far smaller than any that have been devised to date.

The fruits of research are only realized if the public has access to and can understand the information it generates. A groundbreaking effort to improve the Internet connectivity on selected American Indian reservations and Alaska Native villages in the Pacific Northwest is facilitating access of Native Americans living in rural, remote areas to health and biomedical information available over the Internet. NIH is also developing a clinical trials information system to provide patients, families, and members of the public with easy access to information about clinical research studies, including which clinical trials are currently recruiting patients, where the trials are being conducted, what the purpose of the study is, what the criteria are for participating, and who to contact for additional information. NIH is also leading an international effort to provide malaria researchers in Africa with full access to the Internet. Another advance in this area is the development of a teaching module on human genetic variation to enhance the genetic literacy of high school students. A story of discovery outlined the genesis of MEDLINE, a medical reference database, which is now being adapted to serve the public as well as it has served scientists and health professionals for many years. In addition, the *Profiles in Science* Web site contains archival collections of famous medical researchers, allowing the public to get a ›behind the scenes‹ look at the research process.

A number of other discoveries for this Goal related to diagnostic tools or ways to measure disease progression and response to therapy. For instance, studies on early identification of hearing impairment in newborns indicate that three different measures of hearing work equally well, and that a significant group of infants whose hearing is normal at birth appear to lose

hearing in their first year of life. Scientists also devised a new method to test the endurance of the respiratory muscles in patients with chronic obstructive pulmonary disease. The method is less stressful and more reliable than previous methods and has the potential to change clinical practice for the large number of patients with chronic obstructive pulmonary disease.

Other outcomes related to monitoring health and health care. For instance, a new classification system for rehabilitation patients can recognize differences in quality of care while monitoring costs. This first-of-its-kind system should help improve health care quality for seniors, children, and others with disabling conditions by providing alternative payment modules for inpatient rehabilitation services. Another outcome described how scientists found that critical aspects of an extensive State monitoring program aimed at measuring farm worker exposure to pesticides were inaccurate, often underestimating exposure by as much as 40 percent. As a result of these findings, the State regulations were revised to require standardized procedures for monitoring workers exposed to organophosphate and carbamate insecticides. Advanced modeling techniques were used to construct a dynamic model that more accurately estimates the numbers of immigrants who move back and forth across the U.S.-Mexico border. More accurate prediction of population increases and immigrant movement will be a useful tool for researchers, health care providers, and policymakers in the years to come.

Table 6
Titles of NIH Research Outcomes Provided for Goal B
(Develop New or Improved Instruments and Technologies for Use in Research and Medicine)

SCIENCE ADVANCES

$ Teaching a Computer to Diagnose Airway Disease
$ Novel Imaging Technology for Joint Disorders
$ A New View of the Eye
$ Early Identification of Hearing Impairment
$ The Hearing Aid Clinical Trial: A Multicenter, Double-masked Study of Hearing Aid Benefits
$ Cochlear Implants
$ Bioengineering
$ Breakthroughs in Assisted Reproductive Technology Have Many Applications
$ Functional Arteries Grown In Vitro
$ New Strategy Shows Potential for Drug Delivery and Gene Therapy
$ Stem Cell Enhancement Offers New Avenue for Gene Therapy
$ A New Screening Tool for Lung Cancer
$ Strategies for Mapping Common Human Disease Genes
$ Telemedicine--Quality Health Care at a Distance
$ Imaging Live Embryos with Two-Photon Microscopy
$ Rapid, Comprehensive Analysis of Protein Complexes
$ Magnetic Resonance Imaging of Cartilage May Aid Early Diagnosis and Treatment of Osteoarthritis
$ New Models for Migration Patterns into the United States
$ Sequencing the Human Genome, Our Genetic Instruction Book
$ DNA Sequencing Technology: Faster, Better, Cheaper
$ SNPs: New Tools for Tracing Inherited Diseases
$ The Complete Sequence of the Yeast Genome: Simplifying the Study of Complex Biological Processes
$ Chromosome Healing in Embryonic Stem Cells
$ Alcoholic Women Suffer Greater Brain Loss
$ Visualizing the Activity of Respiratory Pacemaker Cells in the Mammalian Brain
$ Enhanced Threading Method for Protein Structure Prediction
$ GeneMap98 Provides a Scaffold for Human Genome Project Data by Mapping 30,000 Human Genes
$ HIV-1 Subtyping Tool Simplifies the Detection of Mosaic HIV-1 Genomes
$ dbSNP: A Database of Single Nucleotide Polymorphisms
$ HIV Alters the Kinetics of T Cells

SCIENCE CAPSULES

$ Ultra-Small Porous Materials Synthesized
$ Keeping Track of Memory T Cells

Science Capsules, continued
$ Measuring Quality of Medical Care
$ New Respiratory Muscle Endurance Test Less Stressful, Potentially More Accurate
$ Growing Evidence of New Bypass Options
$ New Compound for Studying Brain Receptors for Nicotine May Lead to Better Treatments for Several Diseases
$ Cortical Cartography for the 21st Century
$ Profiles in Science
$ Clinical Trials Database
$ Tribal Connections
$ Internet Connectivity Performance Evaluation
$ Measuring Time-Related Changes in Brain Activation
$ Flow Cytometry Enables Rapid Genome AFingerprinting@
$ Powerful New Tool for Drug Discovery
$ Human Sequencing Quality
$ Genetics Resources on the Web (GROW)
$ Genetics Education Resources
$ A New Approach to Tissue Engineering: DNA Delivery via Polymer Matrices
$ Improving Farmworker Monitoring Systems
$ First Chemical Molecular Motor Developed
$ Advances in Structural Biology
$ Life Without Fat
$ Role of T Cells In Hepatitis C
$ Cn3D 2.5 for Structural Analysis
$ PHI-BLAST: Motif-Constrained Sequence Similarity Searches
$ SAGEmap: Measuring Gene Expression
$ Human Genome Resources
$ AT-hook Found in Many Chromosomal/DNA-Binding Proteins
$ DNA Replication May Have Evolved Twice
$ KARIBIN: Karyotypic Region-Based Integration of Chromosomal Information
$ Multilateral Initiative on Malaria

STORIES OF DISCOVERY
$ Artificial Skin Offers Hope for Burn Victims
$ Turning Blue Babies Pink
$ The Visible Humans
$ MEDLINE: A Continuing Story of Discovery
$ Neuroprosthetic Devices
$ Synchrotrons Illuminate Atomic Architecture of Life
$ The DNA Chip
$ Opening a Window on the Brain

GPRA Working Group Assessment of NIH=s Performance: Goal B

The Working Group was charged with assessing NIH=s performance under Goal B. Their specific assignment was to review the research outcomes provided by the NIH and, by applying the assessment criteria (Table 7), determine whether NIH successfully met the goal, substantially exceeded the goal, or failed to meet the goal.

Table 7: Goal B Assessment Criteria

The NIH biomedical research enterprise ***has successfully met this goal*** when its research yields new or improved instruments and technologies for use in research and medicine, and the instruments and technologies are published and/or disseminated or made available to appropriate populations.

The NIH biomedical research enterprise ***has substantially exceeded this goal*** when, in addition to fulfilling the above criteria, any of the following apply:

$ instruments and technologies improve quality of life. This includes new or improved ways to ameliorate/manage symptoms, relieve suffering, and restore/increase physical function/activity.

$ technical barriers are overcome so that investigations that were previously impossible are now possible.

$ instruments and technologies enable novel approaches to answering important biological and behavioral questions.

$ instruments and technologies are applicable to other disciplines, areas of research, or diseases.

$ new/improved methods for generating, organizing, and disseminating genomic and other biological and behavioral information are developed.

Assessment Summary

In their discussion, described below, members of the Working Group identified a number of important themes or categories of research outcomes, discussed the significance of these types of findings, and highlighted a number of research outcomes that they judged to be especially noteworthy. The Working Group concluded that NIH had substantially exceeded the goal of developing new or improved instruments and technologies for use in research and medicine. Specifically, the Working Group concluded that FY99 research outcomes have significantly contributed to progress in developing new or improved instruments and technologies. The new or improved instruments/technologies, as well as new applications of existing instruments/technologies, are enabling researchers to answer important biological questions.

Knowledge gained from the use of these instruments/technologies will underpin the development of new and improved diagnostics, treatments, and preventive strategies that will ultimately improve human health and quality of life.

Assessment Discussion: Research Outcomes and Their Significance

The Working Group also highlighted a number of especially noteworthy outcomes that, in the judgment of the members, demonstrated fulfillment of the criteria for having substantially exceeded the goal. These advances fell into three broad categories: imaging technologies, tools for interpreting genetic information, and technologies for improving the quality of life.

Imaging Technologies. The Working Group observed that a number of the important outcomes provided for this goal are in the field of imaging. It was noted that imaging technology has made enormous progress in the last 10 years and that some of the biggest advances have been in the past two years, as underscored in the science advances and capsules.

Two imaging advances were considered very important for cancer diagnosis and prevention. The ability to teach a computer to locate tumors in the air passages of the lungsCthrough the use of simulated endoscopies, mathematical analysis, and image processing methodsCwas touted as a clearer way of using very fast computed tomography (CT). The significance of the method is that it may allow physicians to diagnose tumors of the airway without the need to pass an instrument down a patient=s throat to see the tumor directly. It will be important to ascertain whether this noninvasive method has other applications, such as detection of colon polyps which are precursors to colon cancer.

Related to this advance is a new screening tool for lung cancer, which uses spiral CT to detect tumors of the lung more effectively than chest x-rays. The opportunity to use spiral CT to safely and reliably screen for lung cancer offers new hope to those who are at increased risk for this disease. The cost of this technique is only slightly more than conventional chest x-ray. In addition, elective surgery of small stage 1 lung cancers is less costly than treating later-stage lung cancers. Routine screening with spiral CT has the potential to reduce the number of lives lost to lung cancer by facilitating diagnose at an earlier and possibly more curable stage. One Working Group member spoke from experience that lung cancer diagnosis can be very unpleasant for patients, and methods such as these tests are not only less invasive, but also provide better data than conventional technologies.

The use of adaptive optics to achieve the clearest view yet of the living retina of the human eye was described by one Working Group member as >optics made adaptive= to see into normal and diseased human eyes. When looking into the eye, adaptive optics allow one to have a much sharper image of the retina than previously possible, to the point of resolving single cells. This technology makes it possible to examine the integrity of photoreceptors and other cell types deep

in the retina of the living eye, to track the progression of a number of retinal diseases such as retinitis pigmentosa, and to evaluate the efficacy of rescue of cell types in the retina. Also, just as adaptive optics can be used to remove the aberrations for light leaving the eye when viewing the retina, it can also be used to remove aberrations for light entering the eye resulting in optics of unprecedented clarity. It was also suggested that this advance offers the possibility of tracking changes in aging eyes and developing ways to accommodate such alterations.

Two-photon microscopy is another imaging advance that the Working Group found impressive and demonstrative of having exceeded Goal B. With confocal microscopyCthe ›precedent= for this new microscopyCone can look at a detailed ›optical slice= of tissue in real time without being hampered by what is happening elsewhere in the tissue or cell. Some problems with traditional confocal microscopy that were identified include the fact that the confocal optics cannot penetrate very deep into a sample and the need for short-wave, high-energy to excite the fluorescent indicators, which can kill or injure the sample. Two-photon microscopy offers a number of important advantages. Because the light is provided by two photons instead of one, only half the energy is required, which is gentler on samples. Two photons are also more penetrating, so researchers can peer deeper into a cell or tissue. This technology has broad application in many areas of biology, from tracking cell migration and gene expression during embryonic development to following cancer cell metastasis in living tissue. In addition to imaging, one group member noted, local biological delivery devices might be manufactured that release a useful compound within a sample when hit by two photons. For example, molecules can be manufactured to release calcium ions or ATP when hit with two photons. This would be a very useful research tool.

The outcome involving magnetic resonance imaging (MRI) for detecting subtle degenerative changes in cartilage was also singled out as evidence of exceeding Goal B because it may aid early diagnosis and treatment of osteoarthritis. This technology uses new sodium MRI, whereas conventional MRI is done with hydrogen molecules; this was hailed as a whole new world of MRI, allowing details to be seen far better than with conventional methods. This promising new imaging method could enhance the ability of physicians and researchers to intervene with appropriate therapeutics, monitor clinical outcomes, and evaluate potential new therapies, including cartilage-protecting drugs and gene therapies.

Tools for Interpreting Genetic Information. The Working Group also was impressed with improvements to DNA sequencing technologies that have allowed the Human Genome Project (HGP) to more quickly decipher the genetic instructions found in our DNA. The group hailed the tremendous speed with which the HGP operates as an enormous leap that will bring significant benefits. These technologies include high-throughput sequencing using automated capillary electrophoresis, which sequences DNA more rapidly with less human intervention, and technologies that integrate sample preparation and DNA sequencing into a single machine. One group member also pointed out that this advance was a cooperation between industry and the

public research sector. The importance of the completion of the yeast genome sequence was also noted.

Another advance that was cited as exceeding Goal B is the rapid, comprehensive analysis of protein complexes. New methods to identify individual proteins within intricate protein complexes will greatly increase the speed at which important protein complexes are analyzed, thereby reducing costs and advancing science more rapidly.

Another important advance that was pointed out was the enhanced Athreading@ method for predicting protein structure. With the sequences of most of the genes in the human genome expected within the next year, the ability to reliably model the protein products of these genes could quickly yield thousands of models for protein structures which would take years to determine by conventional techniques. Any of these model structures might well prove to be the key to deciphering the cause of a human disease.

Technologies to Improve the Quality of Life. The use of cochlear implants to improve speech and speech perception was noted as giving the deaf population a way to become part of mainstream society. A Working Group member who had worked with deaf children and had witnessed the difference that cochlear implants can make in the life and education of a child felt that this advance was the most important thing that has come along for the hearing impaired in many years. It was noted that many in the deaf population can benefit from cochlear implants, particularly the newer devices.

The importance of recent breakthroughs in assisted reproduction technology was also noted. These breakthroughs have many applications beyond infertility treatments. For example, the technologies can potentially be combined with genetic engineering and gene therapy methods, enabling very early treatments of genetic disease; the preservation of rare and endangered species, as well as unique animals; and the development of better models of human disease, especially in species more closely related to humans.

The group also commended a new antibody-based strategy for delivering drugs and gene therapy to the lung. It was thought that, in combination with bioengineering, this would have broad applications as the Human Genome Project comes to completion and was a significant step in the direction of blood stem cell enhancement and gene therapy. This technique may also be applicable to a variety of target cells, including tumor cells or HIV-infected cells. Also, this technique has potential for gene therapy in blood vessels since preliminary data show that DNA linked to the antibody complex can be efficiently internalized by the cells that line vessels.

Many in the group lauded telemedicineCthe use of telecommunications technology for medical diagnosis and patient careCas an important medium for delivering medical services to sites that are at a distance from the provider. NIH=s evaluation of the uses of telemedicine in a wide

variety of settings will help in determining how we can best use information technology for clinical decisions-making. Telemedicine provides an important opportunity not only for American medicine, but also for clinical applications worldwide, as digital imagery can be transmitted anywhere on the globe. Telemedicine will allow physicians to bring significant screening applications to people who are not near urban centers where such screening takes place now. It was further recognized that telemedicine is also useful for nursing care. Several members had already seen telemedicine at work, and noted that it is even being used to perform surgery from several miles away. Another advantage of telemedicine is the ability to obtain advice from distant experts, such as radiologists and cardiologists, to ensure that important findings are not missed.

Functional arteries grown in vitro were also considered an important breakthrough. Many patients have diseased arteries that are badly diseased and no longer able to transport blood. Blood vessels from the patient=s own body can be used to graft onto important arteries, but after several operations, the patient may not have any working vessels to spare. If this advance were to be used with human cells, it could allow researchers to grow new arteries from the patient=s own cells to replace clogged arteries, and not have to worry about an immune response or a shortage of adequate grafts. Importantly, this technology has the potential to benefit thousands of patients.

The research outcome describing a classification system for measuring quality of medical care was also noted and considered important because it is extremely difficult to measure quality. Blood stem cell enhancement was also highlighted as an important accomplishment, since it may be used to treat sickle cell anemia and potentially a great many other diseases.

This page left intentionally blank

CHAPTER 4

Goal C: Develop New or Improved Approaches for Preventing or Delaying the Onset or Progression of Disease and Disability

Introduction

Disease and disability exact enormous tolls on our society, both economic and personal. Rising health care costs highlight the importance of research that seeks to prevent disease and disability, or to delay and/or minimize its impact. In the quest for effective and efficient means of disease prevention, knowledge about basic mechanisms of illness and health must be complemented by public education programs aimed at health-promoting lifestyles and practices.

The development of preventive, delaying, or disease-halting strategies requires a multi-disciplinary approach. Epidemiologic studies provide a necessary foundation for any disease prevention program by identifying the magnitude, and possibly the variability, of a disease within any given population. The epidemiologic patterns of targeted diseases may identify subpopulations that are at risk for developing specific diseases, as well as provide information about the course of disease development in different environments and in different age, racial/ethnic, and socioeconomic groups. Prevention and disease-halting strategies also require a solid understanding of disease mechanisms. For example, it is important to know what causes the disease, how the disease affects specific cells or organs, if there is a genetic basis or predisposition for developing the disease, and whether a person=s immune system plays a role in the disease process. A solid understanding of the disease mechanism facilitates the development of effective ways to prevent or delay the disease. Evaluating any new therapies or behavioral approaches requires clinical research and often clinical trials. Behavioral studies are also needed. Effective strategies for prevention or control of a disease may include a new medication, or an alteration in behavior or lifestyle. Strategies are needed to both educate the public as well as encourage the public to take advantage of these findings.

Targeting preventive and disease- or disability-delaying health interventions to at-risk individuals, as opposed to the general population, permits efficient use of health care dollars, a consideration that will assume increasing importance as baby boomers age and as the ability to identify at-risk populations increases. Researchers understandably are assigning high priority to studies that will identify risk factors for disability, predict disabling events, sharpen screening

processes to identify target populations, and design and evaluate interventions specifically for individuals at risk for disability and disease.

Overview of the NIH Research Outcomes Provided for Goal C

The NIH Institutes and Centers submitted 89 science advances, science capsules, and stories of discovery, that, in their judgment, demonstrated the successful development of new or improved approaches for preventing or delaying the onset or progression of disease and disability (see Table 8).

A number of the discoveries focused on measuresCmany of them prenatalCfor preventing disease and disability in infants and children. One outcome, for example, described a finding that children born to mothers with untreated hypothyroidism during pregnancy scored significantly lower on IQ tests than children of healthy mothers. Thus, early detection and treatment for hypothyroidism of the mother during pregnancy might be an important factor in the intelligence and well-being of her child. And, hypothyroidism might be added to the group of correctable maternal conditions that can influence the long-term health of the child. Researchers found that two thirds of infant homicides occurred by the sixth month, and they also identified factors that contribute to infant homicide, including being the second or later child of a teenage mother, lack of high school education for the mother, and no prenatal care. These findings suggest that interventions which teach behavioral skills and provide social support to teenage mothers are needed prior to the birth of the infant.

Another outcome indicated that maternal smoking was associated with significantly increased rates of drug abuse/addiction among adolescent daughters and conduct disorder among sons, underscoring the need for smoking prevention and cessation programs in women during pregnancy. Analysis of blood from newborns later diagnosed with cerebral palsy indicate that the immune system, whether reacting to infection before birth or by autoimmune reactions, may play a previously unrecognized role in causing cerebral palsy. This discovery may open new approaches to preventing cerebral palsy by focusing on the potential role of immune function in causing this disorder. Another outcome suggested that early initiation of breast-feeding in infants in developing countries may markedly reduce diarrhea throughout the first six months of life.

Several advances addressed the prevention of preterm birthCa major cause of low birth weight, which contributes to infant death and disability. One outcome presented evidence that, although bacterial vaginosis has been consistently associated with an increased risk of preterm birth, treatment of this condition will not reduce preterm birth. This finding has immediate implications for public healthCwere it not for these convincing results, many thousands of pregnant women might have been exposed to a powerful antibiotic without any prospect of benefit, adding unnecessary costs to the health care system. Researchers also found that the body=s immune response to low level genital infections may be a risk factor for premature birth

and they identified a rare genetic change in a component of the immune response that correlates with premature delivery. Based on these results, a genetic test may be developed to diagnose the predisposition to premature birth and there is also the possibility of new drug development as a preventive.

Outcomes related to the prevention of problem behaviors and the encouragement of healthy behaviors were also provided for this goal. A program called ›Going Places= is a school-based intervention program targeting problem behaviors among middle-school students. Students exposed to the program were significantly less likely to smoke, engage in aggressive or deviant behavior; had fewer friends who engaged in problem behaviors; had less positive expectations regarding cigarette use; and reported less increase in parent-adolescent conflict than non-participants. A low-cost, short-term family intervention to enhance general parenting skills and discourage child drug abuse was also determined to be effective in rural family settings and shows great potential for application to communities around the country. Another finding was that visits by nurses to homes of children at risk for developing criminal behavior (children born to teen mothers, single mothers, substance abusing parents, and others) can reduce that behavior in the teen years. Another advance noted that brief counseling of teens seen in emergency room while under the influence of alcohol reduced the incidence of later alcohol-related problems.

Several outcomes addressed the factors that affect health-promoting behaviors. For example, researchers assessing the factors that influence young urban black men to seek and remain in care for hypertension found that nurse-community health worker teams can positively influence follow-up care. Another finding was the identification of differences in the health-promoting behaviors of black and white caregivers, a first step toward individualizing interventions that enable caregivers to continue in their role, and to remain healthy with high quality of life.

Some of the Goal C advances involved strategies for reducing behavior that place a person at increased risk for HIV infection. For example, a number of outcomes described HIV risk reduction strategies that were successful in various study populations, including women in low-income housing developments, black youth, people with serious mental illness, port workers in Brazil, and another group of low-income urban women. Along related lines, one advance identified personality factors that are related to HIV risk behaviors, such as high neuroticism and low conscientiousness.

Many other HIV-related outcomes focused on biological and pharmaceuticalCrather than behavioralCfactors, for reducing HIV transmission and progression. For example, the risk of transmission of HIV from mother to child was found to be approximately 50 percent lower among women who delivered via cesarean section before onset of labor and rupture of membranes, compared to women who delivered by other means. The likelihood of transmission was further reduced with the administration of antiviral drugs. In another advance, scientists demonstrated the safety and effectiveness of the anti-AIDS viral drug nevirapine for preventing

mother-to-child transmission of HIV. Nevirapine is 70 times less expensive and much easier to administer than AZT, the standard of care in the U.S. It offers new hope for reducing maternal-child HIV transmission in developing countries and may be useful for further reducing mother-to-child transmission of AIDS in the U.S. Other research suggested that strategies for reducing HIV viral loads in a woman=s blood during pregnancy can reduce the transmission of HIV from mother to child.

Another outcome described a finding that, in individuals with both malaria and HIV infection, malaria treatment can reduce the quantity of HIV present in the bloodstream. Yet other findings strongly suggested that treatment of sexually transmitted diseases (STDs) before the spread of AIDS within a population can prevent the enhanced transmission of HIV infection. Thus, in developing countries, renewed malaria and STD control efforts may be critical to slowing the progression of HIV infection and may reduce the rapidity of transmission of the AIDS virus. An outcome from a study in Kenya documented that a specific immune factor (IL-10) generated in response to other sexually transmitted diseases is found in the genital tract and appears to enhance vulnerability to HIV infection. This study clarifies our understanding of how infection with non-ulcer forming STDs increases the risk of acquiring AIDS.

Researchers have devised a vaccine candidate that, when tested in a mouse model, induced protective neutralizing antibodies to many strains of HIV. Although the finding is preliminary, it suggests that development of a broadly protective vaccine for HIV may be possible. One outcome described that circumcision before the age of 12 reduced the risk of HIV infection in men, but that circumcision after age 20 did not protect against infection and, therefore, should not be considered as a preventive public health measure. Another outcome identified strategies that can aid in adherence to medication regimens for HIV-infected adults. Another outcome described findings that will be significant for HIV prevention strategies that target injection drug users. Researchers determined that HIV can survive and possibly be transmitted over a 30-day period through contaminated syringes, and that heating drug >cookers= for at least 15 seconds inactivates the HIV virus.

Some advances featured strategies to prevent tobacco use. For example, a 15-session school-based program successfully reduced smoking initiation and reduction in smoking in minority girls. In another finding, community policies to reduce access by youth to tobacco significantly reduced daily smoking by youth compared to communities that did not institute such policies. Another study showed that exercise can aid women in quitting smoking.

A number of the discoveries for Goal C highlighted advances in the prevention of mental illness. Several advances focused on depression. Depression is often unrecognized in adolescents, but one outcome highlighted findings that depression in adolescence can lead to suicide or long-term disability later in life. A study with urban Hispanic girls showed that interpersonal psychotherapy can be an effective treatment for adolescents with depression. Young people are

also particularly susceptible to panic disorder, according to another advance, underscoring the need for early treatment. Recurrent depression can be debilitating, and one outcome noted factors that can help predict who will or will not experience a recurrence of depression, which can aid in determining the amount and duration of treatment for the initial episode.

Several advances noted ways to help prevent mental illness in the elderly. For example, one study identified the mental health needs of people over 60, and clarified the need for primary care practitioners to be more vigilant for psychological issues in the ›mix‹ of their older patients‹ problems. In another outcome, researchers developed multicomponent targeted intervention strategy for preventing delirium in hospitalized older medical patients. This is a significant accomplishment, as delirium is a common and serious source of morbidity and mortality among hospitalized older patients.

Mental illness can accompany other serious illnesses. For example, up to one-half of women diagnosed with metastatic breast cancer may experience clinically significant levels of post-traumatic stress symptoms, suggesting that inadequate and aversive social environments may critically exacerbate the effects of the cancer on women‹s adjustment to their illness and may affect their treatment and recovery. Other investigators found that people aged 65-and-older who have coronary artery disease and also suffer from major depression are twice as likely as their non-depressed counterparts with heart ailments to report problems in basic activities of daily living. Findings such as these emphasize the importance of vigilance, recognition, and targeted interventions for mental illness co-morbidities.

Cancer prevention was a significant topic among the Goal C discoveries. Breast cancer prevention was highlighted in a number of advances, including findings that prophylactic mastectomy and oophorectomy (removal of the ovaries) were associated with 90 and 40 percent reductions in risk of breast cancer, respectively, in women at high risk for the disease. Other outcomes addressed the effectiveness of tamoxifen in reducing breast cancer risk in women at high risk for the disease. The addition of tamoxifen to lumpectomy and radiotherapy in women with ductal carcinoma in situ was also determined to reduce the risk of both cancer recurrence in the same breast and later cancer in the other breast. Still other outcomes identified factors that can predispose a woman to breast cancer, including high levels of estrogen and testosterone, and certain mutations in the genes BRCA1 and BRCA2.

Breast cancer was not the only type of cancer addressed in the outcomes for this goal. One advance indicated that an anti-parasitic drug (oltipraz) reduces the risk of subsequent liver cancers in high risk populations exposed to aflatoxins, which are potent liver carcinogens that are consistent (and often unavoidable) contaminants of the food supply in some parts of the world. This finding represents an important chemoprevention regimen for an environmentally-induced cancer. Another outcome highlighted the development of a mouse lung cancer model which led to the finding that a combination of two specific chemopreventive agents significantly decreased

the incidence and size of tobacco smoke-induced lung cancers. Progress in preventing cervical cancer was also described in a story of discovery.

Several discoveries featured under Goal C contribute to general health and quality of life. A number of outcomes, including a story of discovery, focused on the benefits physical activity, including improvement in physical activity, lower blood pressure, and body fat; improved health and strength and reduced disability in older adults; as well as the usefulness of a simple heart rate-based method for selecting appropriate exercise intensity. Another advance indicated that social and productive activitiesCsuch as church attendance, travel, gardening, community workCconferred survival advantages to the elderly just as much as fitness activities. Another outcome noted that programs to promote healthy diets and regular physical activity in children maintain an effect long after the programs themselves have terminated, indicating that healthy habits are hard to break. Other outcomes included ›Planet Health,= an intervention to reduce obesity among girls; a simple, non-invasive method to determine the proper placement of feeding tubes; and a finding that, since teens need over 9 hours of sleep nightly, school opening times may contribute to sleep-deprivation and increased risk for poor performance and injuries.

Many advances focused on prevention of disability. For example, one outcome was that testosterone replacement could help protect many older men with low testosterone levels against common diseases of aging such as diabetes, heart disease, and osteoporosis. The important role of vitamin D in preventing bone fractures in postmenopausal women was also described in an outcome. One advance noted that a specific chemical that activate a ›redundant gene= may potentially prevent or treat the severe neurological abnormalities observed in X-linked adrenoleukodystrophy. In a more ›basic= outcome, animals with detached retinas demonstrated less retinal cell death and greater cell integrity when maintained in a high oxygen environment for several days. Since oxygen treatment can be easily administered in physicians' offices, hospitals, and homes, further research in this area may lead to a new approach to delaying the progression of cell damage in retinal detachment in humans. One story of discovery recounted the studies that led to the determination of optimum level of calcium intake, which may prevent bone loss, decrease osteoporosis, and prevent fractures. Another story of discovery described the transitional care model, a system for providing comprehensive care for older adults after hospital discharge, which reduces re-admissions and health care costs.

A number of discoveries focused on the prevention of cardiovascular disease. Several advances demonstrated an important connection between physical activity and cardiovascular health. For example, one study showed that even small amounts of energy expended while at work, such as walking up and down stairs rather than taking the elevator, can result in cardiovascular benefits for women. Another advance noted that some differences in blood pressure and cholesterol responses to exercise in older men are related to variations in three different genes, which may help in determining which persons are likely to improve these risk factors with exercise. One advance in the prevention of cardiovascular disease noted that postmenopausal women using

estrogen replacement therapy had a lower degree of stiffness in their carotid arteries, a potential risk factor for cardiovascular disease. Another study showed that naturally occurring fatty acids can prevent vascular inflammation, a critical step in the development of atherosclerosis. Low doses of aspirin were shown to reduce the risk of strokes after surgery to remove fatty deposits from carotid arteries. Another outcome noted that lowering high blood pressure reduced enlargement of the left ventricle of the heart, a substantial risk factor for cardiovascular disease.

Prevention of infectious disease was also featured in this goal. Many of the outcomes related to progress in vaccine development, including for Shigella, a major cause of dysentery in children; drug-resistant strains of the bacterium *Staphylococcus aureus*, which causes widespread hospital- and community-acquired infections; otitis media, or middle ear infection; influenza; and HIV. Another outcome noted that vaccination appears to be the only comprehensive measure to prevent rotavirus infection on a large scale.

Several Goal C outcomes highlighted prevention of chronic illnesses. Researchers were able to immunize diabetes-prone mice with fragments of a pancreatic protein, preventing the development of disease. This finding offers hope that it may one day be possible to immunize children to prevent the development or progression of type 1 diabetes. Two advances noted progress in the prevention of osteoarthritis (OA). One reported that OA patients with the greatest knee instability have the weakest relationship between muscle strength and physical functioning, suggesting the need to treat OA early. The other found that, while women are two times more likely to have hand OA than men, grip strength was found to be an associated factor more for men with hand OA than for women. Because hand OA is common in older Americans, research on risk factors could have significant preventive implications. An advance in asthma interventions found that counseling on reduction of exposure to asthma-causing agents led to reduced asthma episodes. Another outcome described a finding that, after kidney transplantation, prophylactic treatment with valacyclovir prevents cytomegalovirus disease, a major complication of organ transplantation.

Table 8
Titles of NIH Research Outcomes Provided for Goal C
(Develop New or Improved Approaches For Preventing or Delaying the Onset or Progression of Disease And Disability)

SCIENCE ADVANCES

$ Lowering Mother-To-Child Transmission of HIV Through Cesarean Delivery
$ Pharmacological Gene Therapy for X-linked Adrenoleukodystrophy
$ Hypothyroidism During Pregnancy Linked to Lower IQ for Child
$ Planet Health: A Successful Obesity Intervention Among Youth
$ A*Going Places*:@ Promise in Preventing Problem Behavior
$ Identifying Contributors to Infant Homicide
$ Treatment of Bacterial Vaginosis May Not Prevent Preterm Birth
$ Progress in Developing Vaccines Against Infectious Diseases in Children
$ Recruitment of Young Urban Black Men to Clinical Trials
$ Determining Accurate Placement of Feeding Tubes
$ Women=s Cardiovascular Risk Factors on the Job
$ Health-Promotion Behaviors of Black and White Caregivers
$ Simple Lifestyle Changes Can Boost Physical Activity and Cardiovascular Health
$ Researchers Discover How Long HIV Can Survive in Drug Paraphernalia
$ Maternal Smoking During Pregnancy Increases the Risk that Offspring Will Have Conduct Disorders, ADHD and Will Use Drugs
$ Cost Effective Addiction Prevention Program for Rural Families
$ Breast Cancer Risk Reduced in Women at Inherited Risk for the Disease Who Choose Prophylactic Surgery
$ Tamoxifen Reduces Breast Cancer Risk in Women at High Risk
$ Depression in Adolescence
$ Exploring Psychosocial Treatments for Depressed Adolescents
$ Young People are Most Susceptible to Panic Disorder
$ Redefining The Need For Mental Health Care Among Older Americans
$ Changing Women=s Behavior to Prevent Disease
$ Home Visits By Nurses When Children Are Young Reduce Criminal Behavior In Later Years
$ Home-based and Group Exercise Programs Can Improve Health and Functioning of Healthy and Frail Older Adults
$ Prediction of Healthy Aging and Disability-Free Life Expectancy
$ Testosterone Replacement for Older Men with Low Testosterone Levels May Have Protective Effects Against Age-Related Diseases
$ Insights Regarding Recommended Physical Activity for Older Persons
$ Postmenopausal Estrogen Has a Positive Influence on Carotid Artery Stiffness
$ Multicomponent, Targeted Interventions Prevent Delirium in Hospitalized Older Patients

Science Advances, continued

$ Links between AIDS and Malaria: Minimizing Transmission of AIDS
$ A Study of the Safety and Effectiveness of the Anti-AIDS Viral Drug Nevirapine in Infected Pregnant Ugandan Women and their Newborn Children
$ Progress toward Development of a Broadly Effective HIV Vaccine
$ Peptide-Based AImmunization@ Holds Promise to Prevent or Treat Type 1 Diabetes
$ Vitamin A Reduces Mortality of African Children with AIDS
$ Combination HIV Vaccine Induces Diverse Immune Responses in High HIV-Risk Population
$ Novel Antigen May Provide Basis for Vaccine Against Antibiotic Resistant Bacteria Involved in Hospital- and Community-Acquired Infections
$ Cancer Genetic Studies
$ Natural Fatty Acids Might Play Key Role in Preventing Heart Attacks and Strokes
$ Blocking the Action of a Human Liver Carcinogen
$ Chemoprevention of Tobacco Smoke-Induced Tumors

SCIENCE CAPSULES

$ Alcohol and Adolescents: Capturing the Teachable Moment
$ Knee Instability in Strength Training for Relief of Knee Osteoarthritis (OA)
$ Grip Strength and Hand Osteoarthritis (OA)
$ Survival Rates for Patients With Mycosis Fungoides
$ Cerebral Palsy Associated with Inflammatory and Immune Responses
$ Benefits of Low-dose Aspirin for Stroke Prevention
$ The Prevention of Infection (Cytomegalovirus) After Kidney Transplantation
$ Oxygen May Limit Damage in Retinal Detachment
$ Noise-Induced Hearing Loss: Both Common and Preventable
$ Otitis Media
$ Breast-feeding and Disease Prevention
$ Preventing Diarrhea Caused by Rotarvirus
$ High HIV RNA Levels Major Risk Factor for Mother-to-Child HIV Transmission
$ Healthy Habits Are Hard To Shake
$ Lower Blood Pressures Mean Smaller Hearts
$ HIV-1 Viral Load Differences in Men and Women May Call for Earlier Treatment for Women
$ Curtailing Smoking in Minority Girls
$ Effects of Community Policies to Reduce Youth Access to Tobacco
$ Treatment for Ductal Carcinoma In Situ
$ Efficacy of Exercise as an Aid for Smoking Cessation in Women
$ Reducing HIV-Risk for African American Adolescents Through Abstinence and Safer Sex
$ Impediments to Medication Adherence Among HIV-infected Adults
$ Traumatic Stress Associated with a Diagnosis of Metastatic Breast Cancer May Be Relieved by Mental Health Care
$ Evaluating Approaches to Reducing Risk for HIV Infection in People with Serious Mental Illness

Science Capsules, continued

$ Major Depression Reduces the Quality of Life for Patients with Coronary Artery Disease
$ It-s 9:00 P.M. Have You Tucked Your Teen In?
$ Reducing HIV Risk Among Women
$ Encouraging International Research on AIDS Risk Reduction
$ Recurrence of Episodes of Major Depression
$ Social and Productive Activities Confer Survival Advantages to the Elderly
$ Differences in Blood Pressure and Cholesterol Responses to Exercise in Older Men are Related to Genetic Variation
$ High Levels of Estrogen and Testosterone in Women are Associated with Risk of Breast Cancer
$ HIV Risk Behaviors Can Be Predicted from the Five-Factor Model of Personality
$ Genetics of Breast Cancer
$ Low Vitamin D Levels and Bone Fractures in Women
$ Male Circumcision Lowers the Risk of AIDS Infection
$ Impact of Vitamin A on AIDS
$ Presence of Other Sexually Transmitted Diseases Increases AIDS Virus Transmission
$ A Genetic Factor Associated with Premature Delivery
$ STD Treatment and AIDS Virus Transmission
$ Intervention Programs Reduce Asthma Severity

STORIES OF DISCOVERY

$ The Fight Against Influenza Receives a Shot in the Arm
$ Nevirapine - A Global Weapon to Battle Maternal-to-Infant HIV Transmission
$ Preventing Cervical Cancer
$ Using Tamoxifen to Prevent and Treat Cancer
$ Optimal Calcium
$ Exercise: A Fountain of Benefits
$ Evolution of a System for Providing Comprehensive, Coordinated Post-Hospital Care

GPRA Working Group Assessment of NIH=s Performance: Goal C

The Working Group was charged with assessing NIH=s performance under Goal C. Their specific assignment was to review the research outcomes provided by the NIH and, by applying the assessment criteria (Table 9), determine whether NIH successfully met the goal, substantially exceeded the goal, or failed to meet the goal.

Table 9: Goal C Assessment Criteria

The NIH biomedical research enterprise *has successfully met this goal* when its research yields new or improved approaches for preventing or delaying the onset/progression of disease and disability, and the findings are published and/or disseminated.

The NIH biomedical research enterprise *has substantially exceeded this goal* when, in addition to fulfilling the above criteria, any of the following apply:

$ findings demonstrate potential to lead/contribute to the development of preventive measures or strategies for delaying the onset/progression of disease and disability.

$ research-based advances and public health campaigns result in broad health impactsCsuch as reductions in morbidity and mortality, changes in health-related behavior, amelioration of health disparities.

$ prevention strategies are applicable to other disciplines, areas of research, or diseases and conditions.

$ discoveries improve quality of life by preventing or delaying the onset/progression of symptoms, suffering, loss of function, and/or injury.

Assessment Summary

In their discussion, described below, members of the Working Group identified five important themes or categories of prevention-related outcomes, discussed the significance of these types of findings, and highlighted a number of specific research outcomes that they judged to be especially noteworthy. The Working Group was equally divided between judgments that the NIH had met or substantially exceeded the goal. Specifically, the Working Group concluded that the FY99 research outcomes represent a significant contribution to progress in developing new or improved approaches for preventing or delaying the onset of disease and disability. The research outcomes demonstrate NIH responsiveness to health needs and scientific opportunities and innovative uses of technologies. The new or improved preventive strategies that have and will arise from this research will ultimately improve human health and quality of life and have the potential to reduce health care costs.

Assessment Discussion: Research Outcomes and Their Significance

In an initial general discussion, the Working Group acknowledged the importance of considering burden of illness in identifying especially noteworthy outcomes. They emphasized the importance of delaying the onset of disability and the tremendous implications this has for society in terms of health care costs and the toll on caregivers. The number of people that might be affected by an intervention is equally significant, and simple interventions that have an impact on large populations are especially meaningful.

The Working Group also highlighted a number of especially noteworthy outcomes that, in the judgment of the members, fulfilled the criteria for having substantially exceeded the goal. These advances fell into a number of broad categories: longitudinal studies; studies related to the prevention and treatment of mental illness across the life span; therapeutic interventions that also prevent or slow disease progression; behavioral interventions; and community-based interventions.

Longitudinal Studies. The Working Group acknowledged that a number of the studies described in the research outcomes were impressive for their longitudinal perspective. They noted that longitudinal studies are extremely important, providing a valuable window into normal and abnormal human development, and permitting the study of the precursors, onset, progression, and sequelae of disease and disability. The Group recognized that longitudinal research requires continuity in funding over many years without intervening conclusions or measurable outputs along the way, and they commended the willingness of NIH to invest in such studies in a number of different areas.

The outcome that maternal smoking during pregnancy can have long-term negative effects on offspringCdrug abuse/addiction in girls and conduct disorder in boysCwas important for a number of reasons. The findings identify a group at high risk for substance abuse. They also underscore the need for smoking prevention and cessation programs in women during pregnancy. In addition, the findings are consistent with the working hypothesis that nicotine exposure during critical developmental periods may predispose the brain to subsequent addictive influences because of its effect on the dopamine system.

The outcome on the long-term effects of nurse home visitation on children=s criminal and antisocial behavior was also considered noteworthy. Antisocial behaviors among children, are on the rise, and have been for more than a decade. Many researchers, educators, and physicians have proposed that stronger prevention efforts be focused on these children, but the question has remainedCwill such efforts to prevent or reduce antisocial behavior in childhood really work? This encouraging study confirms that prevention *is* effective in the risk-laden lives of young, poor, disadvantaged children. Teenagers born to the women who received the home visits had less problemsCthey managed to avoid or limit their use of illegal drugs, cigarettes, and alcohol;

had fewer sexual encounters, school expulsions, and arrests for any sort of criminal activity; and tended to make more constructive and life-enhancing choices.

The outcome describing results from a 25-year study of Japanese-American men in Hawaii was also demonstrated the importance of longitudinal studies. Because a number of baseline measurements were taken of these men in mid-life, it was possible to identify predictors of long life expectancy and prevention of physical disability. Factors that impair active life are of prime importance as the population ages worldwide. These factors can be treated. While the results suggest that successful intervention can occur at older ages, the study also suggests that preventive and/or therapeutic interventions are optimally initiated at younger ages.

Prevention and Treatment of Mental Illness Across the Life Span. The Goal C outcomes included a number of significant breakthroughs in understanding adolescent depression. For example, researchers found that interpersonal psychotherapy, like cognitive behavioral therapy, can be as effective a treatment for adolescents with depression as it is for adults. For many years, major depression was thought to affect only adults. Thus, the full range of treatments that we now haveCmedications and psychotherapiesCwere developed for, and proven useful in, depressed adults. We now understand that many adolescents also suffer from major depression and know that, for these teens, depression can lead to drastic life-threatening actions, such as suicide or violent behavior; impair development and quality of life; cause conduct problems; and increase the likelihood the teen will experience recurring depressions as an adult. It is therefore critically important that depressed adolescents be treated promptly and with treatments that are both age-appropriate and effective. Interpersonal psychotherapy appears to be acceptable to teens and could become an important approach for reducing depression among adolescents.

Another notable outcome was relevant to a pressing questionCwhat are the actual mental health needs of people older than 60 years of age. Researchers confirmed that mental health problems are not only common among older people, but the specific nature of those problems differ from what emerges in younger individuals. Depression still ranks very high as an issue among the elderly, but so do dementia, alcohol abuse and dependence, and bipolar disorder. Observation and management of these concerns will go far toward controlling costs of care, particularly given the very effective tools now available to primary care practitioners.

Findings about the onset, natural progression of, and recovery from panic disorder were considered important. Investigators determined that panic disorder only rarely begins after mid life, is most apt to begin when a person is young, and is often the outgrowth of a pre-existing anxiety. Appropriate treatment can reduce or prevent panic attacks in 70-90 percent of cases. This has important economic and quality of life implications. A panic attack often mimics the symptoms of a heart attack or other life-threatening medical condition, necessitating the immediate use of extensive and costly medical procedures to rule out these conditions. In

addition, people with panic disorder develop other anxiety disorders such as phobias, which further restrict and impair their lives.

Pharmacological and Diagnostic Interventions. The Working Group noted the range and importance of studies that have provided improved prevention—through pharmacological and other non-behavioral means—across a wide spectrum of disease, from AIDS to rare inborn errors of metabolism. Members acknowledged that NIH has been making an enormous contribution to reducing mortality and improving health around the world. They also emphasized the importance of, and commended NIH=s willingness to support, studies that focus on low- and lower-cost interventions.

The finding that using the chemical 4-phenylbutyrate to activate redundant genes may potentially prevent or treat the severe neurological abnormalities observed in X-linked adrenoleuko-dystrophy (X-ALD) was considered particularly impressive. In children, it may lead to severe disability and often death before ten years of age. Those with a less severe form of X-ALD, which mainly involves the spinal cord, may survive to old age. Currently, there is no good treatment for the disorder=s impact on the nervous system. This type of pharmacological gene therapy could also have clinical application in treating disorders related to the peroxisomes, as well as other inborn errors of metabolism.

An outcome with implications for low-cost prevention included a finding that differences in blood pressure and cholesterol responses to exercise in older men are related to variation in three specific genes. This finding begins to explain the observation that exercise improves cardiovascular disease risk factors, such as blood pressure and cholesterol, but the size of these effects varies widely among persons. These results suggest that determining individuals= relevant genotypes may help identify which persons are likely to benefit most from exercise training.

The outcome that described development of a simple method to determine proper placement of feeding tubes could have remarkable implications for the health, quality of life, and health care expenditures for the one million patients or nursing home residents who are tube-fed each year in the U.S. The new method, which is quicker and less costly than the current use of x-rays, accurately identified all instances of placement of the feeding tube in the respiratory tract, an event which has consequences of high morbidity and mortality, and avoided attendant discomfort to the patient.

The finding that tamoxifen reduces breast cancer risk in women at high risk was also considered outstanding. Breast cancer is the most common cancer in women, and the second leading cause of cancer death. In 1999, an expected 175,000 women will be diagnosed with breast cancer, and approximately 43,300 women will die of their disease. The results provide evidence that the risk

of human cancer can be reduced with a pharmacologic intervention and provide an alternative to Awatchful waiting@ or surgery for women who are at high risk of developing breast cancer.

In another exemplary outcome, scientists demonstrated the safety and effectiveness of the anti-AIDS viral drug nevirapine for preventing mother-to-child transmission of HIV. Nevirapine is 70 times less expensive and much easier to administer than AZT, the standard of care in the United States. It offers new hope for reducing maternal-child HIV transmission in developing countries and may be useful for further reducing mother-to-child transmission of AIDS in the U.S.

Another notable outcome documented that vitamin A supplementation can significantly reduce AIDS- and diarrhea-related deaths among children in developing countries. Vitamin A supplements are inexpensive and easy to distribute. Given the severity of the AIDS epidemic in developing countries, especially the large number of children infected with the AIDS virus, there is an urgent need to find affordable ways to help reduce the impact of this disease. Programs that provide vitamin A supplementation to communities where malnutrition is common could be useful in reduce the mortality from AIDS in children and benefit the health for all children participating.

Behavioral Interventions. A new school-based intervention program called Planet Health, which targeted voluntary behaviors associated with obesity among children and youthCsuch as watching television, eating high fat food, decreased intake of healthy foods, and physical inactivityCwas also lauded by the Working Group. Because the risk of adult obesity is increased if one is significantly overweight during adolescence, interventions to reduce obesity among young children and adolescents are particularly important. The success of this program in public schools, implemented by regular classroom and physical education teachers, also indicates that this promising approach to reducing obesity can be widely adopted.

A number of noteworthy outcomes highlight findings that adults of all ages can derive substantial health benefits from moderate physical activity during leisure time. Changing from a sedentary lifestyle to an active one is estimated to cut the risk of developing cardiovascular disease in half. People have more opportunities to add physical activity to their daily life than they might think. By incorporating the results of this research into their daily lives, Americans can immediately begin to improve their health and cardiovascular disease risk. In addition, employment policies which provide incentives to increase physical activity, especially among women, may result in improved cardiovascular benefits as well as improved morale and reduced health care costs in the short and long term.

A multicomponent, targeted intervention strategy effective for the prevention of delirium in hospitalized older medical patients was deemed quite significant. The intervention prevented the initial development of delirium and reduced the total number of days of delirium. Delirium, or

acute confusional state, is a common and serious source of morbidity and mortality among hospitalized older patients. It is of particular importance because patients over age 65 account for more than 48% of all days of hospital care, and the incidence of delirium will probably increase with the aging of the population. Previous intervention studies of delirium focused on the treatment of delirium rather than on primary prevention. This is the first large-scale clinical trial targeted toward prevention of delirium.

An outcome that identified contributors to infanticide was also considered noteworthy. Homicide is the leading cause of infant death due to injury in the U.S. and rates of infant homicide are increasing. Infants are more likely to be killed than older children, possibly because of their behavior, such as crying and physical vulnerability. The timing of these deaths indicates that interventions which teach behavioral skills and provide social support to teenage mothers are needed prior to the birth of the infant.

Community-Based Interventions. Members of the Working Group noted that a number of the research outcomes demonstrated the important and excellent work NIH has done in the area of community interventions. They also emphasized the importance of, and encouraged, increased efforts to translate them into applications for even larger populations.

One notable outcome highlighted that prevention programs which engage women from impoverished inner-city neighborhoods in community-based HIV prevention activities can bring about reductions in high-risk sexual behaviors. Changing sexual behavior is the best way to prevent infection with HIV in women. AIDS is now a leading cause of premature death for American women. The women most likely to become infected are poor ethnic minority women; although only 21 percent of U.S. women are African American and Hispanic, approximately 77 percent of AIDS cases in women are from these minority groups. Although this research focused on women at risk for HIV, the intervention model can also be adapted for other population groups and other behaviors detrimental to health.

A finding that alcohol-using adolescents seen in emergency rooms subsequently experience fewer alcohol-related problems if they receive brief interventions by counselors at the time of their ER visit was also highlighted by Working Group members. By their senior year of high school, more than 80 percent of adolescents have consumed alcohol. Counselors in this study used empathetic, reflective, nonconfrontational techniques, such as reviewing the circumstances that led to the ER visit and establishing goals that would prevent future incidents.

CHAPTER 5

Goal D: Develop New or Improved Methods for Diagnosing Disease and Disability

Introduction

Early diagnosis and detection of disease is often a key requisite for effective treatment and prevention of disease and disability. Some of the most life-threatening diseases and disabilities can only be controlled or cured if they are diagnosed and treated in the earliest stages. Diagnostic methods include a broad array of biomedical technology, e.g., machines that directly visualize the body, cells, and tissues; instruments that can measure specific body functions; and tests that detect minute quantities of biological and inorganic materials. Despite the extreme variability, diagnostic tools must be accurate and safe. It is also advantageous if they are inexpensive, noninvasive, easy to use and pain-free.

Research to create new diagnostic tools is closely intertwined with basic disease research; diagnostic tools are most commonly developed after the mechanisms of the specific disease process are understood. Studying the efficacy and accuracy of diagnostic tools requires clinical research. It must be shown that a given test is both reliable and effective.

Overview of the NIH Research Outcomes Provided for Goal D

The NIH Institutes and Centers submitted 52 science advances, science capsules, and stories of discovery that, in their judgment, demonstrated progress in the development of new or improved methods for diagnosing disease and disability (see Table 10).

Diagnosis is the first step to both preventing and treating disease. These outcomes reflect quests to understand and to define, in a scientifically exact and predictive way, what disease is and how it progresses. A number of the discoveries represented new understanding of the mechanisms of diseaseCthat is, a clearer understanding of what proteins and other molecules are involved, how they interact, and how they are influenced and regulated. For instance, researchers recently identified a biochemical pathway that has never before been implicated in the origin of hereditary tumors. Specifically, they discovered the function of the MEN1 gene and identified a protein that it interacts with and regulates. Mutations in the MEN1 gene contribute to a large fraction of both inherited and sporadic neuroendocrine tumors. As a result of these discoveries, physicians

will soon be able to screen families at risk for endocrine cancer more easily because activation or inactivation of the gene could be used as a diagnostic tool in the management of cancer. The discovery of the gene also provides a target for the design of drugs to prevent or treat benign and malignant tumors.

Researchers have also made substantial contributions to understanding normal and abnormal functions related to preeclampsia, a life-threatening condition in pregnant women. One team of investigators uncovered the basic mechanisms involved in the normal formation of blood vessels between the placenta and uterus and showed that certain aspects of these mechanisms are different in preeclampsia.

Other advances in understanding the mechanisms of disease revealed critical details in the pathways that lead to the development of brain aneurysms, Alzheimer=s disease, asthma and hypertension in children, and infection-induced hearing loss. New understanding of the causes and courses of these disorders and conditions lay the foundation for developing not only new diagnostic capabilities, but also new avenues for prevention and treatment.

A number of other outcomes highlighted the association between genes and disease and how this is leading to new and improved methods of diagnosis. For example, after two decades of work, scientists have now identified genes and proteins which are altered in the tumor cells of a form of primary central nervous system lymphoma that affects the eyes. By using a relatively new technique called microdissection, researchers can remove tumor cells from the eye to look for the altered genes as a new way of diagnosing this cancer. The identification of genes and gene alterations that are associated with disease or susceptibility to disease helps researchers to understand the mechanism of the disorder, which in turn can lead to improved diagnostic, treatment, and prevention strategies. The Goal D outcomes also featured such strides for Hermansky-Pudlak syndrome, a hereditary disorder characterized by albinism; type II diabetes; alcoholism; brain tumors; hereditary and age-related hearing impairments; and lung cancer. Clearly, genetic analysis is a promising approach to diagnosis.

By no means did all outcomes that described improved diagnostics focus on genes. For example, investigators discovered that certain cytokines, which are proteins that stimulate or inhibit immune cells, are elevated in eyes with primary intraocular lymphoma. Another outcome described a finding that the different forms of the human enzyme known as alcohol dehydrogenaseCwhich functions in alcohol metabolismCinfluences the rate at which the body clears alcohol. These findings could lead to methods of identifying biological variations that put people at risk of alcoholism.

One Goal D outcome described new information and practical diagnostic tools for making an early differential diagnosis between early stuttering and normal speech, and for identifying different subtypes of stuttering and the risk of developing persistent stuttering. These findings

will help to focus selective treatment for children who are most likely to have persistent stuttering, which causes serious impairment in verbal communication that is often associated with significant emotional and social adjustment difficulties. Another outcome featured the development of an effective blood test to detect pheochromocytomasCrare, benign tumors of the adrenal gland which can cause persistent high blood pressure. The test is based on the detection of two chemicals produced at high levels by an enzyme present in the tumors. The ability to identify or exclude a pheochromocytoma should greatly increase the efficiency, and decrease the cost of, diagnostic evaluation of patients with high blood pressure and findings suggestive of a pheochromocytoma.

Finally, advances in technology distinguished another important category of outcomes. New tools, such as computers, computerized analytical programs, and imaging instruments often facilitate the development of diagnostic tests that are more sensitive, easier to perform, and less invasive. More than a dozen of the Goal D research outcomes related to how computers and other instruments can play a critical role in diagnosis. For example, the use of a new sodium MRI technique to image cartilage deterioration will aid in the noninvasive diagnosis of osteoarthritis. In another outcome, scientists used advanced nuclear magnetic resonance technology to reveal structural abnormalities in two proteins that aid blood and bone development. Because abnormalities in these proteins have been implicated as contributors to acute human leukemias and other developmental disorders, the ability to detect them will have important prognostic implications that can guide the selection of therapy and should hasten the development of highly specific, and hence less toxic, forms of leukemia therapy. Other scientists used MRI volumetric imaging technology to measure changes in brain volume that are predictive of conversion of mild cognitive impairment to Alzheimer=s disease. One outcome detailed that investigators developed and evaluated an imaging technique that enables detection of dopamine-specific neurons. This new methodology will be useful in diagnosing Parkinson's disease, which is characterized by severe depletion of neurons that release the neurotransmitter dopamine, which is needed for normal movement and muscle control. By developing techniques to detect early loss of such neurons, scientists hope to enable timely intervention that will prevent further deterioration or even restore lost neurons through use of embryonic system cells.

Positron Emission Tomography (PET) neuroimaging techniques were proved successful in obtaining the first evidence in humans that there is a direct association between dopamine D2 receptor levels in the brain and the pleasurable effects of psychostimulants. That is, for the first time, the number of receptors has been correlated directly with the Apleasantness@ of a drug. These findings have significant implications for individual differences in how much a person likes a drug and may represent a critical component in the neurobiological basis for drug abuse and addiction vulnerability.

One outcome described how researchers developed and published a method to use simulated endoscopies to automatically locate tumors in the air passages of the lungs. Their methods are

based on the abnormal shape of airway tumors, use mathematical techniques developed by 19th century mathematicians, and build on more recent image processing methods developed by mathematicians and computer graphics specialists. This new method may allow physicians to diagnose tumors of the airway without the need to pass an instrument down a patient=s throat to see the tumor directly. Other investigators employed a relatively new imaging technology known as optical coherence tomography to detect small structural changes that occur in cartilage during the earliest stages of joint disorders such as osteoarthritis. Refinement of this technology and its ultimate clinical use may permit early diagnosis of degenerative joint disorders, evaluation of disease severity and progression, and enhanced understanding of pathological processes within joints.

Imaging technologies are not the only useful diagnostic technologies featured in the Goal D outcomes. For example, one outcome described an international collaboration that resulted in a new PCR-based method to rapidly and accurately define the virus responsible for dengue in Central America. This technique is a simple, one-step process using widely available chemicals and can be done in the country where the disease is found. Using this new information, the researchers were able to track the movement of the dengue virus from Asia and Africa to the Americas. Another outcome featured the use of DNA microarray technology to compare the genetic material of different bacteria that cause tuberculosis and to identify regions of DNA that are present in one bacterial strain and absent in others. The information from these studies could lead to rational approaches for the design of improved tuberculosis diagnostics and vaccines.

Table 10
Titles of NIH Research Outcomes Provided for Goal D
(Develop New or Improved Methods for Diagnosing Disease and Disability)

SCIENCE ADVANCES

$ Blood Test to Detect a Curable, Dangerous Cause of High Blood Pressure
$ Detection of Genes and Proteins from Lymphoma Cells Can Simplify the Diagnosis of Primary Intraocular Lymphoma
$ *In vivo* Imaging of Tumors in Mice with Protease-Activated Near-Infrared Fluorescent Probes
$ Patients with Mild Cognitive Impairment Can Be Clinically Characterized for Treatment Interventions
$ Hippocampal Volume MRI Predicts Conversion of Mild Cognitive Impairment to Alzheimer=s Disease
$ Genome-wide Search for Type 2 Diabetes Susceptibility Genes
$ Novel Brain Scanning Technique Detects Parkinson-like Condition
$ Dengue in Central America
$ A Specific Indian AIDS Virus Strain
$ Development of Guidelines for Cystic Fibrosis Carrier Genetic Screening
$ New Gene-Knockout Mice Reveal Role of Enzymes in Alcohol Metabolism
$ Scientists Trace Origins of Finns, an Informative Population for Genetics Studies
$ Chromosome 16 May Contain a Gene that Contributes to Alcoholism
$ BTGAPCThe Brain Tumor Genome Anatomy Project
$ Molecular Rescue Mission Unveils Genetic Link to Common Birth Defect
$ Mechanism of Action of Endocrine Tumor Formation
$ Identification and Characterization of Genes which Cause Hereditary Hearing Impairment
$ Genetic Associations in Age-Related Hearing Thresholds (Presbycusis)
$ Congenital Cytomegalovirus (CMV) Infection and Sensorineural Hearing Loss
$ Early Childhood Stuttering
$ Defining a Phenotype for Specific Language Impairment
$ Understanding the Causes of Hermansky-Pudlak Syndrome
$ Daylight Sets the Biological Clock through Photoreceptors Unrelated to Vision
$ Sleep Apnea in Early Childhood is Associated With Asthma and Hypertension
$ Imaging Agent May Provide Information about Recovery after Revascularization
$ Why Do Some People Like Addictive Drugs?
$ Nerve Cell Growth And Development Studies Open Window To New Diagnostic Techniques
$ Association of Gene Polymorphisms, Tobacco Carcinogens, and Lung Cancer
$ New Technology Provides Molecular Basis of Tuberculosis Pathogenesis and the Potential for Rational Design of New Vaccines and Diagnostics
$ Hypohidrotic Ectodermal Dysplasia
$ Teaching a Computer to Diagnose Airway Disease
$ Novel Imaging Technology for Joint Disorders

Science Advances, continued
$ Early Identification of Hearing Impairment
$ A New Screening Tool for Lung Cancer
$ Magnetic Resonance Imaging of Cartilage May Aid Early Diagnosis, Treatment of Osteoarthritis
$ Hypothyroidism During Pregnancy Linked to Lower IQ for Child
$ Determining Accurate Placement of Feeding Tubes
$ Guidance for Treating Patients with Brain Aneurysms
$ Understanding the Causes of Preeclampsia
$ Biomolecular Underpinnings of Acute Human Leukemias

SCIENCE CAPSULES
$ GJB2: A Major Cause of Hereditary Hearing Impairment in the United States
$ Epilepsy Caused by Pig Tapeworms
$ Improved Genetic Testing for Colorectal Cancer Risk
$ Biomarkers for Oxidative Stress Discovered
$ Psychiatric Disorders and Disability in Refugee Survivors of Mass Violence
$ Risk for Depression in Young Women During Transition to Adulthood
$ The Cumulative Toll of Trauma on Mental Health
$ Flow Cytometry Enables Rapid Genome "Fingerprinting"

STORIES OF DISCOVERY
$ Osteogenesis Imperfecta -- Brittle Bone Disease
$ Hereditary Hearing Impairment: Gene Discovery and Issues for Clinical Application
$ Turning Blue Babies Pink
$ A New Form of Type 2 Gaucher Disease

GPRA Working Group Assessment of NIH=s Performance: Goal D

The Working Group was charged with assessing NIH=s performance under Goal D. Their specific assignment was to review the research outcomes provided by the NIH and, by applying the assessment criteria (Table 11), determine whether NIH successfully met the goal, substantially exceeded the goal, or failed to meet the goal.

Table 11: Goal D Assessment Criteria

The NIH biomedical research enterprise ***has successfully met this goal*** when its research yields new or improved methods for diagnosing disease and disability, and the methods are published and/or disseminated or made available to appropriate populations.

The NIH biomedical research enterprise ***has substantially exceeded this goal*** when, in addition to fulfilling the above criteria, any of the following apply:

$ new findings demonstrate potential to lead/contribute to the development of new and improved diagnostics.

$ diagnostics improve health care and/or quality of life. This includes new or improved diagnostic methods that are more sensitive and accurate; allow diagnosis or detection at an early/earlier stage; enable early/earlier treatment or preventive interventions; predict future susceptibility to disease/disability; and/or are less invasive, painful, and/or costly than current techniques.

$ diagnostic methods are applicable to other disciplines, areas of research, or diseases.

Assessment Summary

In their discussion, described below, members of the Working Group identified a number of important themes or categories of research outcomes related to diagnisis, discussed the significance of these types of findings, and highlighted a number of research outcomes that they judged to be especially noteworthy. The Working Group concluded that NIH had substantially exceeded Goal D. Specifically, the Working Group concluded that the outcomes demonstrated that NIH had significantly contributed to the development of new or improved methods for diagnosing disease. The research outcomes demonstrate new or improved diagnostic methodologies that are more accurate, less invasive, and/or more cost-effective, and are responsive to emerging health needs, scientific opportunities, and new technologies. The new or improved diagnostics that have or will arise from this research will ultimately improve human health and quality of life. For example, earlier and/or more accurate diagnosis can lead to earlier and more informed treatment decisions, and this may contribute to more positive health outcomes.

Assessment Discussion: Research Outcomes and Their Significance

In an initial general discussion, the Working Group acknowledged that no one study could adequately portray the long-term and broadly ranging impacts of NIH research in the field of diagnostics. They also discussed important considerations for identifying noteworthy outcomes, including the number of people affected; significance in terms of yielding fundamental new knowledge and facilitating additional research; cost effectiveness; and quality-of-life issues. The Working Group identified four broad categories that encompassed the plethora of studies selected for special commendation. Noteworthy outcomes ranged from developmental issues and disease susceptibility to geriatric concerns and tumor analysis and included improvements in diagnostic tools as well as changes in behavior appropriate for at-risk individuals.

Genetic Diagnosis. The expanding field of genomics paves the way for studies correlating genes with disease or with susceptibility to disease. The Working Group cited several outcomes that provided excellent examples of genetic diagnosis. For example, the identification of a novel diabetes susceptibility locus on human chromosome 1 will help researchers to uncover the molecular basis of this complex disorder, which in turn may lead to improved treatment strategies. Discovery of the underlying genes may also enable early identification of at-risk individuals, who might delay or prevent the onset of disease by making certain lifestyle changes such as exercising more or watching their diet. This is especially significant, given that diabetes mellitus affects an estimated 16 million people in the United States and costs the nation about $105 billion annually in health-related expenditures.

A second example of diagnostic advancement through gene discovery and identification involves analysis of brain tumors by the Brain Tumor Genome Anatomy Project (BTGAP). Currently, BTGAP focuses on genes that are active in gliomas and has been extraordinarily effective in uncovering unique human genes. The Working Group agreed that the BTGAP will be critical in developing a comprehensive molecular profile of primary brain tumors at progressive levels of malignancy. Understanding brain tumors at the level of the genes and proteins that control cell function will be key to developing effective diagnosis and treatment.

Genes can also contribute to disability, and the Working Group called attention to an advance that described the identification and characterization of genes which cause hereditary hearing loss. They noted that a remarkable number of genes and gene alterations had been uncovered that compromise the development of normal spoken language skills. Furthermore, differential forms of some of given genes can confer susceptibility to noise-induced hearing loss or age related hearing loss. Identification of these genes has provided unexpected knowledge of metabolic pathways and structures essential for normal auditory functions. This research generates hope for developing timely and precise diagnoses for hereditary hearing loss.

Another notable outcome illustrated how broad-ranging genetic diagnosis can be. Cystic fibrosis (CF) is one of the most common inherited disorders in Caucasians. The availability of genetic testing for CF has raised important issues such as whether people would be able to understand complex genetic test results when they had no experience with and little knowledge of the disease, genetics, and genetic testing; how people ould respond to an imperfect test; and whether these tests could lead to more anxiety and uncertainty than they relieve. Clinical, laboratory and educational guidelines are currently being developed to address these issues. The Working Group noted that this diagnostic effort will have tremendous impact on the general population and, moreover as increasing numbers of genes associated with a wide range of illnesses are discovered, more genetic tests will become available. This effort provides an important model for the introduction of future genetic testing services.

Modern genetic technology can provides accurate and reliable information rapidly at low cost, allowing its successful use in developing countries to enhance understanding of new and reemerging diseases. Simple, fast and accurate characterization of these diseases is an important step in ultimately finding a cure. For these reasons, a new techniques to characterize dengue fever was also deemed important by the Working Group. Existing methods for characterizing viruses are costly and complicated to do, particularly in developing countries with limited capabilities and resources. This technique is a simple, one-step process using widely available chemicals and can be done in the country where the disease is found. Another important advance cited by the Working Group is the ability to detect genes and proteins from lymphoma cells, which can simplify the diagnosis of primary intraocular lymphoma. Early diagnosis and prompt treatment may improve survival.

New or Improved Diagnostic Technologies. The impact of technology on the ability to diagnose diseases and disabilities cannot be underestimated. Technological advances can not only make diagnosis easier and more reliable, but can allow detection of disease at an earlier stage, enable specific treatments to be initiated, and help prevent invasive, painful, and/or costly procedures. The Working Group felt that several scientific advances in particular deserved highlighting. These scientific advances were chosen to emphasize the role of technology in diagnosis.

A new method to more precisely image tumor cells was considered an important example of diagnostic technology at a fundamental level. Investigators injected tumor-bearing mice with a unique imaging agent (near-infrared fluorescence imaging probes) coupled with a novel substance that moves efficiently into tumor cells. When the agent was internalized into the cancer cells, enzymes within that cell ›activated= the agent and caused it to fluoresce. The fluorescence could then be detected non-invasively. Using this technique, the investigators were able to image tumors smaller than three-tenths of a millimeter in diameter. Although this new technique is in the early stages of development, it shows great promise for the non-invasive detection of very small tumors.

An outcome that highlighted how a computer had been ›taught= to diagnose airway disease was also commended. Not only might this method enable the noninvasive diagnosis of tumors of the airway, but it could be adapted to find tumors in other organs without the need for conventional endoscopy. Two new techniques for early detection of changes in cartilage associated with osteoarthritis were also lauded. Refinement of these promising technologies may permit early diagnosis of and intervention for degenerative joint disorders, evaluation of disease severity and progression, and enhanced understanding of pathological processes within joints and testing of potential new therapies, including cartilage-protecting drugs and gene therapies.

A novel imaging technique for detecting Parkinson=s disease was also noted by the Working Group. This is significant because the early detection of affected neurons may also allow early treatment of the disease. Parkinson's disease is one of the most common neurological disorders, affecting about 1 million Americans. Every year about 40,000 new patients are diagnosed in the United States.

Diagnosis usually refers to identification of the onset of disease, but many diagnostic technologies have important additional potential usesCin monitoring progression of disease and monitoring response to clinical intervention. One exemplary outcome described a new approach to obtaining useful information, prior to revascularization surgery, about the potential for functional recovery in patients with chronic coronary artery disease and left ventricular dysfunction. Treatment decisions will be better informed if physicians can distinguish between potentially reversible regional heart dysfunction and irreversible regional heart dysfunction. More accurate assessment of myocardial viability may result in more individually tailored treatment plans, more appropriate utilization of resources, and enhanced efficiency of health care delivery.

Advancement of Fundamental Knowledge. The Working Group identified a number of outcomes that highlight the importance of fundamental research in identifying disease, not through new technology or the identification of genes, but in expanding the knowledge base on which prognosis depends. Each example demonstrates how development of diagnosis contributes to understanding disease. Diagnosis further aids in characterization and facilitates prognosis of disease and disabilities.

In the field of diagnostic pathology, great effort has been expended toward correlating cellular products with the cancer types. The new finding that altered regulation of cytokine production is associated with primary intraocular lymphoma will allow a more precise diagnosis of the disease, leading to earlier detection and treatment. In addition, learning how the altered genes function in lymphoma cells may provide information that will contribute to new understanding of tumor development and new strategies for effective cancer treatment.

The development of optimal procedures for neonatal hearing screening and acquisition of new knowledge about the onset of hearing impairment will be essential for ensuring more normal development of language skills in hearing-impaired children.

Another example of how diagnostic advances can expands the knowledge base about disease or disability concerns people with mild cognitive impairment (MCI). One outcome described new knowledge about how to clinically characterize patients with MCI for treatment interventions. Investigators found that individuals with MCI differed from unimpaired persons primarily in the area of memory, with other cognitive functions being comparable. Compared to very mild Alzheimer=s disease (AD) patients, the memory of MCI individuals was similar, but Alzheimer=s patients were impaired in other cognitive domains. The study documented the clinical course of MCI individuals with respect to change on standardized tests and diagnostic outcome and demonstrated that the subjects with MCI declined at a rate greater than that of the controls but less rapidly than the patients with mild AD. Importantly, the results also demonstrated that people with MCI are at increased risk of progressing to AD. Another outcome involved the use of volumetric MRI for predicting the conversion of MCI to AD. Given this diagnostic ability to detect early disease, studies can be focused on treatments that stop brain changes before clinical deterioration sets in.

Subtle differences in disease agents make huge differences in treatments. Such may be the case with an Indian strain of human immunodeficiency virus (HIV). The first characterization of the complete genetic code of a AIDS virus strain isolated from infected patients in India revealed what appears to be a hybrid of two previously known strains of HIV. Characteristics of the AIDS virus which are known to be targets of the body=s immune defenses were substantially different in the strains isolated in India compared to the strain most prevalent in the U.S. This new data will facilitate vaccine development efforts in India. According to World Health Organization estimates, India will have the largest number of HIV-infected people by the turn of the century. The diagnosis of which virus they are infected with will be important to determine in order to develop effective treatment.

The BCG vaccine for tuberculosis has evolved into several daughter strains with variable vaccine efficacies against tuberculosis. As cited in the preceding example, diagnosis of the strain of infection is important. One significant outcome highlighted the use of DNA microarray technology for a more efficient method of comparing strains of tuberculosis-causing bacteria. Information from these studies could lead to rational approaches for the design of improved diagnostics and vaccines. By identifying regions in ***M. tuberculosis*** that are missing in BCG, scientists may be able to develop a highly specific tuberculosis diagnostic test that can identify tuberculosis infection even when a person has been vaccinated with BCG. This test would be important for those countries with a low prevalence of disease that wish to introduce vaccines, and also for those countries where BCG is used and a more discriminating treatment of latent

tuberculosis cases is needed. This decade could see 80 million cases of tuberculosis worldwide.

Diagnosis for Quality of Life. The Working Group noted that improvements in the quality of life for individuals is equally important to new understanding of disease and disabilities. Simple new diagnostic tools and improvements in existing diagnostic methodologies can make a fundamental difference in the lives of many people. Working Group members highlighted a number of significant outcomes that demonstrated how diagnostic tools can make peoples lives easier, more productive, and more useful. Moreover, using the established technologies in new ways provides a cost-effectiveness sometimes unbeatable by wholly new methods.

Preeclampsia in pregnant women causes dangerously high blood pressure, kidney failure, and seizures. Moreover, preeclampsia puts the baby at risk for being born prematurely and/or low birth weight. New understanding of the basic mechanisms involved in preeclampsia provides new avenues for early, rapid diagnosis and prevention of a potentially fatal condition. Another notable outcome revealed the importance of monitoring maternal hypothyroidism during pregnancy. Researchers determined that children born to mothers with untreated hypothyroidism during pregnancy scored significantly lower on IQ tests than did children of healthy mothers. Thus, early detection and treatment for hypothyroidism of the mother during pregnancy might be an important factor in the intelligence and well-being of her child.

A simple method for determining accurate placement of feeding tubes was also considered noteworthy. While this finding represents only a minor advance on a technical scale, the tremendous numbers of people in hospitals and nursing homes who are tube-fed (about one million) makes this outcome significant. During and any time after insertion of the feeding tube there is a high potential for displacement such that tube contents are directed into the respiratory tract. This is not only potentially fatal, but results in morbidity and additional health care costs. The new method is quicker and less costly than the current use of x-rays and, as important, can easily avert a great deal of patient discomfort.

CHAPTER 6

Goal E: Develop New or Improved Approaches for Treating Disease and Disability

Introduction

The aim of much of NIH research is the development of new and improved therapeutics. This pathway to our ultimate goal of better health requires a strong foundation of understanding disease mechanisms and normal and abnormal biological functions. Searches for new therapies depend on advances in chemistry, bioengineering, enzymology, structural biology, genetics, immunology, cellular and molecular biology, and pharmacology.

New techniques to rapidly screen chemical compounds are now greatly expanding the pool from which possible therapeutic substances can be drawn. The study of molecular structures by x-ray crystallography has yielded detailed understanding of many molecules critical to health, as well as therapeutic molecules specifically tailored to "fit" the structures and thus alter their chemical activity. In addition, the science of synthetic chemistry has yielded many improved ways to design new therapeutic substances.

Clinical research is the final common pathway to the development of new therapeutics. New approaches, be they drugs, devices, or changes in behavior, must ultimately be evaluated in humans. This usually requires clinical trials. In addition, health services research is needed to study the ultimate effect of any new approach in real life settings.

Overview of the NIH Research Outcomes Provided for Goal A

The NIH Institutes and Centers submitted 91 science advances, science capsules, and stories of discovery that, in their judgment, demonstrated progress in developing new or improved approaches for treating disease and disability (see Table 12). The outcomes represented a broad range of therapies, from medications, surgeries, and medical devices, to behavioral interventions. They also demonstrated the various stages or steps in developing many therapies, from pre-clinical, which often involves animal studies and cell and tissue studies, to progressive stages of human testing.

Stem cell therapies are potential, innovative treatments that marshal the breathtaking power of human stem cells. Stem cells are immature cells that can multiply and specialize to form many types of mature cells. As therapeutic agents, stem cells have the potential to replace cells that are destroyed by disease or injury. Moreover, owing to their seemingly unlimited supply, they can potentially overcome a major problem in health care todayCthe shortage of donor cells and organs. Realization of the vast potential of stem cell therapies has been hampered by many problems, including how to treat the cells before implantation and how to coax stem cells to assume the identity of the mature cells they are needed to replace. A number of the outcomes described how investigators have recently begun to triumph over these obstacles.

For example, a group of discoveries has brought researchers closer than ever before to human clinical trials to repair skeletal defects. In one outcome, researchers used a certain class of stem cells, called bone marrow stromal cells, that have the ability to form bone, cartilage, and other connective tissues. By growing and specially treating the stromal cells in tissue culture before transplanting them, researchers successfully generated new bone in the skulls of mice. Several other outcomes featured animal models of neurological diseases. These furnished the first evidence that stem cells can repair damage from brain disorders in which the degeneration or dysfunction is widespread, rather than in discrete locations. Although these results are promising, several obstacles still remain. These findings need to be replicated with human cells, researchers needs to learn how to grow sufficient numbers of cells for transplantation, and safe methods of obtaining stem cells from adults need to be developed.

Immunotherapy seeks to harness the prowess of the immune system to fight disease. Bone marrow transplants were the first, and thus the most recognizable, of the immunotherapies, but research has branched beyond this in targeting diseases such as immunological deficiencies, infectious diseases, cancer, diabetes, lupus and a host of others. A number of Goal E outcomes featured immunotherapies, including not only bone marrow transplants, but also cytokines and monoclonal antibodies, among others. Early successes with bone marrow transplants have become tempered by awareness that bone marrow transplants may not be the best therapy in all circumstances. For example, in the case of severe combined immunodeficiency, a rare syndrome that kills children usually within the first year of life, one research outcome documented the life-saving potential of bone marrow transplants when given within the first months of life. On the other hand, another outcome revealed that bone marrow transplants were not necessarily ideal for young adults with acute myeloid leukemia. In these patients, researchers found that although bone marrow transplants were as effective as chemotherapy, they were not as safe.

Cytokines are an array of small proteins that regulate the intensity and duration of immune responses. They do so in part by acting as messengers, communicating signals between immune cells typically to activate or suppress an immune response. Several outcomes described findings that cytokines were most effective in combination with other treatments. One, for example, demonstrated that the combination of a cytokine (interferon) and the antiviral drug ribavirin was

more effective than interferon alone for the treatment of hepatitis C virus. This virus is the leading cause of chronic liver disease and is the most common reason for liver transplantation. Another outcome took aim at B cell lymphoma using the cytokine known as granulocyte colony-stimulating factor. Researchers coupled this cytokine with proteins from patients= own tumors to activate their immune systems to destroy the cancer cells. In another outcome, this time with HIV patients, investigators found that the cytokine interleukin-2, in combination with highly active anti-retroviral therapy, led to a substantial reduction in the reservoir of HIV that hides in a particular type of immune cell. This combination treatment has the potential to eliminate latently infected immune cells, an exciting prospect for millions of HIV-infected people worldwide.

In most cases, when an organism makes antibodies against something, the antibodies recognize, and bind to, many different sites on that target, whether it is a protein, bacterium, or subcellular organelle. Monoclonal antibodies are not like this, however. They are exquisitely specific, recognizing and attaching to only one particular feature of a given target. Some of the research outcomes featured the use of monoclonal antibodies for successfully combating disease. This included the treatment of fistulas in patients with Crohn=s disease, a chronic inflammatory bowel disease, and treatment of uveitis, an inflammation of the eye that mainly affects children and young adults and, if untreated, can cause blindness.

Organ transplants have been a mainstay of treatment for many advanced diseases, but new strategies are evolving to improve their performance or to replace them with less invasive approaches. One outcome described a finding that simultaneous transplants of a pancreas and a kidney are more effective than a single kidney transplant alone for patients with Type I diabetes and end stage kidney failure. Other advances related to Type I diabetes helped to refine pancreatic islet cells, rather than a whole pancreas, for transplantation. Islet cells of the pancreas are destroyed by the body=s own immune system in Type I diabetes.

Two other outcomes represented novel and stunning departures from the use of whole organs or tissue transplants. One revealed that a dietary supplement, curcumin (from the same plant as the spice cumin), could repair damaged skeletal muscles in mice. Another advance ventured into the world of polymer chemistry. Researchers developed a technique in animals whereby a liquid polymer containing cartilage cells is injected under the skin and then hardened, or polymerized, by ultraviolet light shone through the skin. Weeks later, this material had begun to form new cartilage. Transdermal photopolymerization could effectively allow implantation of biomaterials for plastic surgery, including both biodegradable and permanent polymers, and potentially enable cells or drugs to be injected and encapsulated for tissue engineering, drug delivery or other applications.

Several outcomes from cancer research demonstrated immediate application or far-reaching potential. Immediate changes in the standard of care for invasive cervical cancer were ushered in by several prominent studies. These demonstrated that chemotherapy plus radiation given at the

same time improved survival of women with cervical cancer. Another advance used a new form of radiation therapy to safely deliver high radiation doses and to control prostate cancer. The new approach is 3-D conformal radiation therapy, which employs sophisticated computer technology to focus the treatment field more tightly and narrowly to the prostate tumor.

A new wave of cancer treatments can be expected to emerge from advances in our basic understanding of cancer mechanisms and the ability of cancer cells to resist chemotherapy. For example, a major problem in the treatment of cancers is acquired resistance of tumors to chemotherapy or radiation therapy. Increasing the concentrations of cytotoxic drugs or the dose of radiation is generally ineffective. One outcome detailed a discovery that resistance to programmed cell death (apoptosis) is the principal mechanism by which tumors to evade these therapies. Furthermore, the investigators found that they could inhibit the molecule responsible for this phenomenon. This inhibition made resistant tumor cells susceptible to chemotherapy or radiation therapy, resulting in tumor shrinkage, and in some cases complete eradication. Another outcome described the development of a promising immunotoxin for treating leukemias and lymphomas. Immunotoxins are specialized molecules that consist of two components: a protein that targets tumor cells, and a poison, or toxin, that is then delivered directly to the cancer cell, killing it.

New medications for addiction and pain treatment were propelled closer to the marketplace, according to several outcomes. One treatment for heroin addiction combines two medications, buprenorphine and naloxone, and a New Drug Application for this combination medication was recently filed with the FDA. In another outcome, the drug, nalmefene, was shown to be safe and effective in a controlled clinical trial for relapse prevention in alcoholics. The search for a nonaddictive pain treatment has been a galvanizing force for many decades. One outcome described a promising new opiate treatment for pain that has been tested in animals. The drug is three times more potent than morphine but does not produce physical dependence. Such a treatment has the potential to surmount the widespread problem of patients being undertreated for pain. Inadequate pain treatment was documented in another advance, which showed that over a quarter of older and minority nursing-home residents in daily pain received no pain medication at all.

A major obstacle to the development of neuropharmaceuticals is the difficulty of penetrating the brain=s own protective shield, the blood brain barrier. This barrier hinders access to many types of drugs. Two outcomes described headway in overcoming this barrier, employing entirely different strategies. One involved the delivery of a pain medication to the spinal cord of animals through the use of gene therapy. Another, developed by neurosurgeons, relies on small tubes introduced into the brain and spinal cord. This method successfully delivered anticancer drugs to malignant brain tumors in patients and drugs to combat Parkinson=s disease in animals. It has the potential to permit precise targeting of drugs where they are needed in the brain and spinal cord,

opening up new opportunities for treating many disorders, including tumors, neurodegenerative diseases, epilepsy, spinal cord and brain injury, and inherited defects like Gaucher=s disease.

Important advances in behavioral treatments for children with mental disorders were also highlighted in the Goal E outcomes. One treatment targeted children with attention-deficit/hyperactivity disorder and involved the combination of medication plus counseling. This multimodal treatment approach was shown to be more effective than medication alone. The second treatment featured an alternative to hospitalization for children with severe mental illness. An intensive home-based program of individualized treatment was shown to be equivalent to or better than hospitalization, and certainly less expensive, for young people with psychiatric emergencies.

Table 12
Titles of NIH Research Outcomes Provided for Goal E
(Develop New or Improved Approaches for Treating Disease and Disability)

SCIENCE ADVANCES

$ New Medication, Nalmefene, Provides Another Option for Alcoholism Treatment
$ Antibiotic Restores Critical Protein Production in Muscular Dystrophy Mouse Model
$ Advances in Systemic Lupus ErythematosusCTreating Mouse Systemic Lupus Kidney Disease with Short Protein Fragments
$ Gene Therapy Restored Protective Function in Limb Girdle Muscular Dystrophy
$ Low Dose Estrogen Prevents Bone Loss
$ Green Tea Products Show Anti-inflammatory Activity in Mouse Models
$ Guidance for Treating Patients with Brain Aneurysms
$ Cut Nerve Fibers Are Repaired in An Animal Model of Spinal Cord Injury
$ Bionic Rats
$ Drug Delivery to the Central Nervous System
$ Stem Cell Transplants Migrate Throughout the Abnormal Brain and Reduce Disease Symptoms
$ Antibiotics Restore Protein Function in Mouse Model of Muscular Dystrophy
$ Gene Therapy in an Animal Model of Muscular Dystrophy
$ New Approach to Treating Pneumonia in Immunosuppressed Populations
$ Control and Prevention of Type 1 Diabetes is Demonstrated in Mice
$ Safe and Effective Delivery of Therapeutic Proteins by Gene Therapy
$ Infliximab for Crohn=s Disease: A Randomized, Blinded, Controlled Clinical Trial
$ The Treatment of Chronic Hepatitis C
$ Growing Body of Evidence Identifies Efficacy of Alternative Pain Management Techniques
$ New Treatment for Uveitis May Improve Vision and Quality of Life
$ Electrical Stimulation of the Paralyzed Larynx
$ Identifying the Most Effective Infertility Treatment
$ Understanding the Causes of Preeclampsia
$ Risk Factors Among Women After Coronary Artery Bypass Grafting
$ Controlling Postoperative Pain with Less Medication
$ Reducing the Burden of Caregivers of Persons with Dementia
$ Successful Ventilator Strategy Found for Acute Respiratory Distress Syndrome Patients
$ Treating Chronic Pain With Fewer Side Effects
$ Treating Chronic Pain With Gene Therapy
$ A New Drug Application Filed with the FDA for a Medication to Treat Heroin Addiction
$ Effects of Behavioral Therapy for Cocaine Addiction Can Be Long-lasting
$ The Key to Addiction Treatment Success: Tailoring Treatment Approaches to Patients= Needs
$ Adolescents Who Inhale Volatile Solvents (such as glue or spray paint) Are More Prone To Delinquent Behavior

Science Advances, continued
$ Therapeutic Vaccine Development for B cell Lymphoma
$ Chemotherapy Plus Radiation Improves Survival of Patients With Cervical Cancer
$ An Alternative To Hospitalization For Children With Severe Mental Illness
$ How Best To Treat Attention-Deficit/Hyperactivity Disorder (ADHD)
$ Forcing Cancer Cells to Commit Suicide
$ Biomolecular Underpinnings of Acute Human Leukemia
$ Transplants Save Lives of Children with Severe Immune Disorders
$ Leishmaniasis: New Insights into Factors Responsible for Disease Severity
$ A Combination of Anti-Retroviral Therapy and Interleukin-2 has Potential to Eliminate the Reservoir of HIV in Resting T Cells
$ Controlling Acquired Chemoresistance of Tumors by Inhibition of NF-κB
$ Dietary Supplement Stimulates Muscle Regeneration after Traumatic Injury
$ Tissue Engineering and Neo-Organ Formation

SCIENCE CAPSULES
$ Testosterone Supplements in Older Men
$ Promoting Tolerance to Ischemia in Stroke
$ Embryonic Stem Cells in Animal Models of Cell Therapy
$ Improved Treatment for Late Stage Parkinson=s Disease
$ Epidemiology of Diabetes Interventions and Complications (EDIC)
$ Simultaneous Pancreas-Kidney Transplantation: Mortality in Type 1 Diabetes and End-Stage Kidney Failure
$ Aminoglycoside-Induced Ototoxicity
$ Old Cancer Therapy May Have New Life
$ Yoga Techniques Show Promise for OCD
$ Ocular Estrogen Receptor Discovered
$ Drug Inhibits Growth of New Blood Vessels in the Eye
$ New Help for Patients with Congenital Nystagmus
$ Mechanisms Involved in Modulation of Uveitis through feeding of Retinal Proteins
$ Head and Neck Cancer
$ Mouse Model May Lead To Treatment of a Common Human Kidney Disorder
$ Early Revascularization Brings Late Rewards
$ New Hope for Hemophilia B Cure
$ Inhaled Antibiotics Benefit Cystic Fibrosis Patients
$ Safe Treatment for Children With Sickle Cell Disease
$ Reducing Cocaine Craving in Animals
$ The Nicotine Antagonist, Mecamylamine, Decreases Cocaine Craving in Crack Users
$ Major Depression and Attention -Deficit/hyperactivity Disorder Increase the Severity of Nicotine Addiction
$ Predicting the Success or Failure of Treatment for Drug Addiction
$ Acupuncture: A Treatment for Cocaine Addiction?

Science Capsules, continued

$ Treatment of Leukemias and Lymphomas with the Immunotoxin LMB-2
$ The Development of Cancer Vaccines
$ Prostate Cancer Treatment
$ Comparison of Treatments for Acute Myeloid Leukemia
$ Adequacy of Psychopharmacological Treatment of Depression Found Wanting
$ Older and Minority Nursing Home Residents with Cancer Experience Inadequate Pain Control Procedures
$ Behavioral Training is More Effective than Drug Therapy for Urge Urinary Incontinence
$ Exendin-4 Improves Insulin Response in Subjects With Type-2 Diabetes
$ Maintenance of Systolic Blood Pressure Within an Intermediate Range May Reduce Memory Loss Among Elderly Hypertensives
$ Defects in Tumor-Protection Protein May Lead to Cancer
$ Development of Alternative Anti-Inflammatory Drugs through Studies of a Coral Enzyme
$ Regeneration of Bone and Marrow by Transplantation of Bone Marrow Stromal Cells
$ Gene Therapy for Pain

STORIES OF DISCOVERY

$ Osteogenesis Imperfecta -- Brittle Bone Disease
$ The Cycle of Life
$ Artificial Skin Offers Hope for Burn Victims
$ Turning Blue Babies Pink
$ Multiple Applications of Gene Transfer to Salivary Glands
$ Using Tamoxifen to Prevent and Treat Cancer
$ Islet Transplantation for Type 1 Diabetes
$ Psoriasis
$ Complementary and Alternative Medicine (CAM): Ever More Popular, It-s a User Friendly Option

GPRA Working Group Assessment of NIH=s Performance: Goal E

The Working Group was charged with assessing NIH=s performance under Goal E. Their specific assignment was to review the research outcomes provided by the NIH and, by applying the assessment criteria (Table 13), determine whether NIH successfully met the goal, substantially exceeded the goal, or failed to meet the goal.

Table 13: Goal E Assessment Criteria

The NIH biomedical research enterprise *has successfully met this goal* when its research yields new or improved approaches for treating disease and disability, findings are published and/or disseminated.

The NIH biomedical research enterprise *has substantially exceeded this goal* when, in addition to fulfilling the above criteria, any of the following apply:

$ new findings demonstrate potential to lead/contribute to the development of new and improved treatments.

$ new or improved treatments improve health care and/or quality of life. This includes treatments that are more effective or have fewer side effects; relieve suffering; are more cost-effective; are less invasive, painful, and/or costly than current methods; effect a cure or remission of disease; and/or restore/increase physical function/activity.

$ treatment approaches are applicable to other disciplines, areas of research, or diseases.

Assessment Summary

In their discussion, described below, members of the Working Group identified a number of important themes or categories of research outcomes relating to treatments, discussed the significance of these types of findings, and highlighted a number of research outcomes that they judged to be especially noteworthy. The Working Group concluded that NIH had substantially exceeded Goal E. Specifically, the Working Group concluded that the outcomes demonstrated significant progress in the development of new or improved approaches for treating disease and disability. The research outcomes also signify NIH=s responsiveness to health needs, scientific opportunities, and development and utilization of new technologies. The new or improved approaches to treatment that have or will arise from this research offer new or expanded treatment options and improved length and/or quality of life for patients. In addition, they may provide more cost-effective strategies for treating disease and disability.

Assessment Discussion: Research Outcomes and Their Significance

In an initial general discussion, the Working Group acknowledged each treatment advance represented the culmination of years—sometimes decades—of groundbreaking research, beginning most often with advances in the basic biomedical sciences. The path from basic science to a new treatment is generally marked by serendipity, high risks, false starts, collaboration, and perseverance.

In addition, while finding the outcomes indicative of having substantially exceeded the goal, the Working Group pointed out NIH=s contributions were in reality much greater than what was represented in the Goal E outcomes. Specifically, they noted that the approach of limiting the outcomes to advances that were published in FY 1999 did not capture all of the progress for which NIH deserves credit. Working Group members also proposed a broader concept of treatment, one which acknowledges that early treatment can prevent or avoid subsequent complications and sequelae, including disability.

Members of the Working Group also strongly endorsed the idea that, in the future, NIH consider as appropriate for inclusion in Goal E those newly licensed treatments for which NIH-supported research made significant contributions. For example, Working Group members considered it likely that many of the drugs and devices approved by the FDA within FY 1999 were critically dependent on years of NIH-supported basic and translational research. Every major advance at the bedside is the product of years of painstaking and uncertain investment in basic and translational research. Some of these journeys were portrayed in Goal E Stories of Discovery. In particular, Working Group members found the 30-year story of tamoxifen=s odyssey, which began in the 1960s as an *unsuccessful* contraceptive, to be illustrative of the promise and pitfalls in the arduous path of a medication to the marketplace. Today, tamoxifen is considered a towering achievement, not just for the treatment of breast cancer but also for its prevention.

Several especially noteworthy advances were highlighted by the Group that, in their judgment, particularly fulfilled the criteria they had established for having substantially exceeded the goal. These advances, discussed below, relate to gene therapy, new uses of antibiotics, stem cell therapy, immunotherapy, and behavioral therapies.

Gene Therapy. Gene therapy refers to the novel treatment of disease through a host of techniques that transfer therapeutic genes (DNA) into recipients. The challenge in gene therapy is to develop ways to safely and effectively deliver these genes. For this purpose, researchers have developed gene delivery vehicles, called vectors, which carry the genes deep inside the cell and ensure integration into patients= own DNA. Yet vector development has been beset by technical problems in penetrating into cells and incorporating into DNA. The results in animal models often have been disappointing—e.g., an insufficient supply of the gene product (a protein) or inadequate control over timing or duration of its production.

One stellar outcome managed to simultaneously solve both these problems of gene delivery. In animal studies, researchers successfully used a harmless version of a viral vector known as adeno-associated viral vector (AAV). What made this vector special was that it carried several genes. One of the genes was for the therapeutic protein (in this case, growth hormone). Others were for parts of a transcription factor that could control the amount of growth hormone produced. But the transcription factor gene was ineffective aloneCit could only switch on growth hormone production *along with a drug* taken by mouth. In other words, the dose and timing of the orally administered drug controlled the action of the transcription factor, which, in turn, controlled the amount produced of the gene product. Thus, without the drug, no growth hormone was produced; with the drug, growth hormone was produced for as long as the drug was taken. The amount produced was exquisitely dictated by the dose of the drug. In addition, because the system is made up of human components, the potential of initiating an immune response in the patient is limited.

The value of the AAV vector in gene therapy was reinforced in another outcome, according to the Working Group. In this advance, the research goal was to correct a defective muscle protein in a form of muscular dystrophy. Limb girdle muscular dystrophy is caused by defects in several muscle proteins, one of which is delta-sarcoglycan. In an animal model of limb girdle muscular dystrophy, researchers employed the AAV vector to deliver the correct gene for delta-sarcoglycan. Their technique showed successful incorporation and expression of the correct gene into a hind limb muscle, a feat accomplished with the aid of histamine to help the viral vector enter muscles from the circulation. This procedure efficiently protected muscle fibers from degeneration. The researchers are now adapting their procedure for human clinical trials.

New Uses of Antibiotics. Antibiotics not only kill infectious agents, but they may also be useful in seemingly inconceivable ways. This was the message that the Working Group wanted to underscore about an outcome featuring the antibiotic gentamicinCthat it has an unexpected new application. Many years= worth of basic research into how antibiotics work had already revealed that gentamicin belongs to a class of antibiotics called aminoglycosides, which have the ability to suppress (overcome) certain gene sequences, called Astop codons,@ that halt protein production.

Here again the treatment was for one of the muscular dystrophies, in this case Duchenne muscular dystrophy (DMD). In this disease, affected males experience progressive muscle degeneration and die of respiratory or cardiac failure in their 20s. About one-third of cases are caused by mutations in the gene for the muscle protein, dystrophin. In a clever advance that involved a mouse model of the DMD, researchers made use of two critical pieces of informationChow aminoglycosides work and also their understanding of the mouse model they were using. Specifically, the reason the mice had DMD was because their dystrophin gene was mutated; it contained a stop codon and thus the mice could not produce complete molecules of dystrophin. When investigators administered gentamicin to the DMD mice, the aminoglycoside overcame (suppressed) the stop codon in the mutated dystrophin gene, restoring dystrophin to the

mouse muscle cells. This discovery may pave the way for a treatment in some human patients with DMD. Just as importantly, this approach might prove to be useful in other diseases in which a protein is defective because of the presence of a stop codon.

Stem Cell Therapy. The advent of stem cell therapies is an outgrowth of years of basic research on stem cells, which have proven very elusive to find. Neural stem cells are a type of stem cell that can multiply and specialize to become mature cell types found in the brain. Several recent findings encourage the hope that neural stem cells might be helpful for disorders in which cell loss is restricted to certain parts of the brain, such as Parkinson=s disease, but their promise has been unexplored for the many brain diseases in which cell dysfunction is >global= or spread widely throughout the brain. Now, a new advance provides the first evidence that neural stem cells can repair global damage. Researchers injected cultured neural stem cells into the brains of newborn >shiverer= mice. This strain of mice is plagued by tremors because they lack the means to produce myelin, the insulation that surrounds nerve fibers. Many of the stem cells migrated throughout the brain and matured into the cells that normally form myelin. In the majority of transplanted mice, the stem cells produced enough myelin for the tremors to have almost completely disappeared. This advance has profound implications for several human disorders marked by deficiencies of myelin, such as multiple sclerosis and childhood disorders called leukodystrophies. Yet many questions remain, such as whether a transplanted stem cells will fall victim to ongoing degenerative disease processes, whether these findings can be replicated with human cells, and whether researchers can develop safe ways to obtain stem cells from the brains of adults.

Immunotherapy. Monoclonal antibodies have begun to fulfill their therapeutic promise after years of mixed, sometimes disconcerting, results. Nowhere is this more apparent than in the treatment of Crohn=s disease, a chronic inflammatory bowel disease. In 1998 a new drug for Crohn=s disease, infliximab, received approval by the FDA. The product grabbed headlines because it was the first-ever approved treatment for Crohn=s disease. Infliximab is a genetically engineered monoclonal antibody against a protein (tumor necrosis factor-alpha) that is excessively produced in Crohn=s disease.

A noteworthy Goal E outcome described an important findingCthat infliximab is also effective for the treatment of fistulas, a serious complication affecting one-third of patients with Crohn=s disease. Fistulas are perforations, or holes, of the bowel wall leading to other tissues such as the bladder, vagina, or skin. They rarely heal spontaneously and, until now, required surgery. This new use for infliximab is a major advance for a condition that affects 500,000 people in the U.S., and it also foreshadows renewed interest in monoclonal antibodies as therapeutic agents.

Behavioral Therapy. Behavioral therapy holds a prominent place in the armamentarium of effective treatments. It is the only form of treatment found effective for certain disorders, such as eating disorders that imperil the lives of adolescents. Behavioral therapy is also an effective

supplement to medications for many other conditions. In fact, one of the outcomes noted earlier demonstrated that a combination of medication and behavioral therapy was more effective than pharmacological therapy alone for children with attention deficit hyperactivity disorder. Behavioral therapy also is critical for those who cannot tolerate the side effects of medications, or for whom medications are ineffective. Finally, it is sometimes the only feasible approach for health promotion and primary prevention, especially for families struggling to care for loved ones with bipolar disorder, schizophrenia, and Alzheimer=s disease. This was underscored by an outcome that featured an educational family group intervention to significantly decrease the burden for family caregivers of individuals with dementia.

The benefits of behavioral therapy were also evident in several outcomes related to the treatment of pain. One advance, for example, should bring welcome news to the 23 million people who undergo surgery in the United States each year. This advance demonstrated the value of music, jaw relaxation, and the combination of the two as adjuncts (additional measures) to post-operative pain medication. These behavioral approaches reduced pain more than patient-controlled analgesia alone on the first two postoperative days after major abdominal surgery. The findings also support recommendations from a government panel in 1992 urging greater use of non-pharmacological interventions for acute pain control.

Other important advances in behavioral therapy were related to the treatment of addiction. Ensuring cocaine abstinence and keeping patients in treatment during and after formal treatment have proved to be quite challenging. One approach has shown promise for these problemsCa behavioral treatment that combines counseling with incentives in the form of vouchers that are exchangeable for retail items. The vouchers are awarded to patients for remaining in treatment and free from cocaine. Until now, researchers have not explored the long-term effects of this combined behavioral approach. One outcome furnished the first demonstration that using counseling and vouchers increased cocaine abstinence during formal treatment and up to one-year later. A final set of notable advances found that a major determinant of effective treatment for cocaine dependence was to match patients to the most appropriate behavioral therapies. In other words, the choice of which behavioral therapy to select should depend on individual factors, such as the severity of the person=s dependence and cultural background.